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PERORAL AND INTRAVENOUS CHOLECYSTOGRAPHY: A COMPARISON OF THE RELATIVE MERITS AND RESULTS IN 100 CASES.*

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The following study is an attempt to determine from the clinical as well as roentgenologic standpoint the relative effectiveness in cholecystography of the two accepted methods of administering the iodin-containing dye; incidentally to establish for ourselves the practicability of the intravenous method for ambulant patients.

The study differs from previously reported comparisons in that the patients were chosen to represent all phases of the gall bladder syndrome. Practically all results heretofore reported have been obtained incidental to a larger series in those individuals who came to operation, and by investigators who were already committed to one or the other method of administration. The reports have shown fairly consistent agreement in positive findings in the obviously diseased gall bladder which demands surgical treatment; and the operation has confirmed both the peroral and intravenous tests in upward of 80 per cent of instances.

The clinician's real problem in gall bladder suspects, however,

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is to determine accurately when to advise surgical treatment in the instances in which symptoms and signs have not yet indicated surgery to patient and doctor alike. If taken in the elective stage, operation obviously prevents much suffering and secondary morbid change in the body. The real diagnostic value of cholecystography therefore lies in its dependability in these less dramatic cases. Consequently, the present series was made to include a majority of mild or indefinite cases in spite of the fact that operative proof was not obtained. In the absence of operation we have checked the accuracy of the two tests against the assembled clinical data and final diagnosis.

Further unprejudiced comparison of the value of the tests is indicated also by the fact that in the 7 years that cholecystography has been in use a distinct cleavage has developed between proponents of the peroral and intravenous methods. The originators[1] and a large number of able examiners use the intravenous technique exclusively. An equally imposing group of clinicians and roentgenologists maintain the superiority of the peroral method.

The former group have consistently held that the unreliability of the peroral method outweighs in importance the technical difficulties of the intravenous. Their position is that the peroral test is of value only if it shows normal gall bladder function, the presence of nonopaque cholesterol stones, or gross deformities of the viscus. In the instances in which the shadow is faint or absent from the roentgenographic films they contend that the interpreter frequently cannot be certain whether gall bladder or test is at fault. The doubt arises from the fact that imperfect absorption of the dye from the intestinal tract, or vomiting or diarrhea which at times follow its ingestion, may play a part in the abnormal result. Asserting that the above variables cannot be eliminated when the dye is given by mouth, and because they are likely to implicate a gall bladder not diseased, that school subordinates the practical difficulties of the intravenous technique to a determination to achieve accuracy.

On the other hand, the proponents of the peroral method feel as strongly that, with proper technique and watchfulness, its unreliability may be minimized; that its simplicity and harmlessness make it therefore the method of choice, especially where large numbers of patients must be handled.

One further factor, that of reaction to the drug, must be considered in an appraisal of the methods. Reactions to the swallowed dye, while they may interfere with the interpretations, are never alarming. Serious or dangerous reactions, on the other hand, have been reported when the dye is injected into a vein. Such have been denied for a large series by Moore[2] who reported recently the experience of $6\frac{1}{2}$ years at St. Louis. Kirklin[3] of The Mayo Clinic, however, who uses the peroral technique, in a recent appraisal of cholecystography, writes: "Occasional serious reactions, even in the

hands of experts, make one hesitate to urge its use (*i.e.*, the intravenous method) as a general routine. . . . Few examiners use it in office practice; the general feeling is that the patient should be hospitalized." Such requirement would of course seriously handicap the intravenous method as a routine measure.

Methods. Our procedure was to choose, during the past year, as they came along for study, 100 patients from the gastrointestinal outpatient section and the medical wards of the hospital, and arrange that each one receive both tests as closely together as possible. Sixty per cent of the group were chosen from among the outpatients in order to establish to our satisfaction that the intravenous test is safe and practicable for ambulant patients. This of course is an absolute necessity if the intravenous method is to compare in practical value to the peroral. Seventy of the patients were women, 30 men. All but 10 received the dye by mouth first. (It was found that the order of the tests had no influence on the interpretations). Most of the patients were gall bladder suspects. In 15 per cent biliary tract disease was not seriously considered and these individuals acted as controls. We excluded from the intravenous group, and therefore from the series, only those patients with marked cardiovascular disease, in whom reaction or sudden fall in blood pressure might lead to accident, and patients in the acute stage of cholecystitis or with common duct obstruction, in whom both tests are valueless.

No modifications of the established technique were made which might alter the interpretations of one or the other test. The department of radiology had previously set 40 gr. (2.6 gm.) of tetiothalein sodium N.N.R. (Iodeikon-Mallinckrodt) as the standard dose of dye adequate for satisfactory shadows by the peroral route. It was given dissolved in water with or shortly after a light evening meal. The first film was made 14 hours later. Tetradol and other preparations had been given thorough trial by the department and no other found so uniform in results. Grape juice as a vehicle had been discarded because it was found often to cause pylorospasm and slow absorption; carbonated water, because some of the dye was apt to be lost in the froth which resulted from the mixture. Data regarding the relative amounts and types of dye used are included in Table 1.

TABLE 1.—METHOD OF STUDY.

	Number and per cent.
Total number of cases studied	100
Interval between tests: Less than 3 weeks	81
3 weeks to 3 months	9
Over 3 months	10
Dye used: Peroral method:	
Tetiothalein-sodium (Iodeikon), 2.5 gm.	100
Intravenous method:	
Phentetiothalein-sodium (Iso-iodeikon), 2.5 gm.	88
Tetiothalein-sodium (Iodeikon), 3.5 gm.	12

For the intravenous test the patients reported in groups of 2 or 3 in the late afternoon. We found for this work, after a trial in 12 cases of the identical dye used for oral administration, that the isomer of tetraiodophenolphthalein, the phentetiothalein sodium N.N.R., or iso-iodeikon, was the more satisfactory. The dye was injected and the effects closely watched for ½ hour by one of us (L. H. H.).

We further diluted the freshly sterilized 8 per cent solution of the drug by injecting it, not directly into the vein, but into the rubber tubing through which a free gravity flow of warm physiologic saline into the vein had been established. This refinement was first suggested by Liest[4] and to us by Dr. Jacob Vastine. By such procedure we hoped to escape the severe reactions which are generally believed due to too rapid administration or too strong a solution.

Each subject was kept recumbent for at least ½ hour after the injection and then allowed to go home or back to the ward as the case might be. Sixteen to 17 hours elapsed between the injection and the first film, whereas in the peroral test the interval was 14 hours. It has been established, however, that there is no constant superiority of shadow at any one time between the limits of 14 and 17 hours, so that the unequal interval before filming need not be considered as unfair to one or the other test. Otherwise the procedure, once the drug was administered, and until the last film had been made, was identical for both groups. Suffice to say that each set of films was reviewed independently by one of us (E. P. P.) without any clinical facts of the case at hand, and a second comparison made.

Results. Three facts stand out as a result of the comparison; First, that the peroral test was inconclusive, in spite of careful technique, in one-third of the cases; second, that the observation of the dye shadow in the intestinal tract was an absolute necessity before the interpreter could make a report of a non-functioning gall bladder on the oral test; and third, that the reactions to the intravenous technique, while not alarming, were such as to necessitate great care in its administration.

In Tables 2 and 3 the results of the parallel series are summarized. One-fourth of the patients had normal cholecystograms by both methods, and in the majority of these the shadows were equally satisfactory for the interpreter. Both tests agreed in showing abnormal function in approximately one-third of the number, making the total of agreement 61 per cent.

Of the remaining 39 per cent the peroral method was 6 times more often inconclusive, for one reason or another. In 27 of the 34 doubtful peroral results, the fault lay with the test and not with the patient. Of the 32 instances (Table 2) where the gall bladder was found to function normally by the intravenous test after the peroral had led to an abnormal or unsatisfactory report, the clinical and

other laboratory data confirmed the intravenous in 25, or 73 per cent. Poor utilization of the dye, with insufficient shadow, and loss of dye due to reactions were, so far as could be determined, the main causes of the inconclusive oral tests. In 3 oral and a like number of the 5 inconclusive intravenous tests, gas in overlying bowel obscured the picture.

TABLE 2.—COMPARISON OF RESULTS.

Normal function by both tests			25
Abnormal function by both tests			36
Peroral inconclusive, intravenous normal function			32
Peroral:	Abnormal function	15	
	Doubtful	12	
	Unsatisfactory	5	
Intravenous inconclusive, oral normal			5
Peroral unsatisfactory, intravenous abnormal			2
Totals:	Tests in agreement		61
	Tests at variance		39

TABLE 3.—RELATIVE EFFICIENCY OF THE METHODS.

Interpretation of the films:			
	Intravenous more satisfactory		46
	Peroral and intravenous equally satisfactory		36
	Peroral more satisfactory		18
Checked by operation			14
	Abnormal or absent function both tests, confirmed	12	
	Both tests normal, calculi at operation	1	
	Peroral, no function, intravenous normal and confirmed	1	

Total Series Checked Against Clinical Findings and Final Diagnosis.

Intravenous test agrees	88
Peroral test agrees	63

The interpreter, as was to be expected, was more often satisfied with the density of the intravenous shadow, when he compared the two. In a considerable number, however, the shadows were of comparable clarity. For a small series, the results reported by others were duplicated, namely, that in the type of case which clinically demands operation, the two tests agree in positive results. The peroral test, however, more often disagreed with the completed clinical workup when the less obvious cases are included.

An added result of the attention paid to the interpretation of the peroral cholecystograms was the confirmation of our previous observations that without homogeneous dye in the intestinal tract a pathologic gall bladder could not be reported even though no sign of the viscus appeared on the films. Delario[5] has recently called attention to the characteristic dye shadow in the gut when the drug has been absorbed and secreted by the liver.

From the standpoint of reactions the advantage rests distinctly with the peroral technique. The figures in Table 4 represent the number of individuals reacting, whose major symptom is recorded. A few had, for instance, headache along with chill and fever, the

latter only being listed. The peroral tests were followed by untoward effects 18 times, the intravenous 54 times, including the thromboses. None of the intravenous reactions were alarming, however. Only 2 of the ambulant patients, 1 with a cirrhotic liver, and the other with a highly unstable nervous system, reacted sufficiently to require overnight hospitalization. There were no delayed reactions of any seriousness and follow-up visits or letters from 60 of the 100 patients indicate that in these individuals at least, no late effects have occurred.

TABLE 4.—REACTIONS.

Peroral method:	Total (nausea, vomiting or diarrhea)	18
	Interfere with interpretation of films	5
Intravenous method:	Total	43
	Urticaria	27
	Chill and fever	6
	Vomiting	5
	Nausea, headache or back pain	5
Local thrombophlebitis at site of injection		11
Blood pressure readings before and after injection in 14 unselected cases:		
	Unchanged	7
	Drop of 5 points	2
	Drop of 5 to 15 points	3
	Drop of 25 points (hypertension)	2

At the beginning a few rather severe chills occurred following the intravenous injections, which we ascribed to the distilled water used for the solutions rather than to the dye. When freshly sterilized Sunbeam water was substituted, that complication was avoided. Urticaria of varying severity was by far the most common reaction, and in 5 instances small injections of adrenalin were needed to control the itching. In spite of the great dilution of the dye (from 150 to 300 cc. of normal saline were used in each case), the vein wall was in a few instances sufficiently irritated to set up a local thrombophlebitis. No great discomfort and no disability resulted from the phlebitis which at the maximum extended only 10 cm. up the arm.

Blood pressure readings before and after the injection were made in a consecutive unselected group which included 2 hypertension cases. The moderate drop in tension was, in our opinion, due more to the patient's relaxation and loss of apprehension during administration of the dye than to its direct action on the vascular or nervous system. The hypertensive patients showed no ill effects whatever. No other circulatory phenomena were observed in this series.

Comment. Peroral cholecystography is a diagnostic method of great usefulness in suspected gall bladder disease. One is led, nevertheless, in the light of the present results to urge again that the clinician consider it as an aid to diagnosis in conjunction with other data, and not as making the diagnosis. Our results emphasize the fact that the peroral test, inconclusive in a third of the series, must

not be accepted as final in doubtful cases. Under such circumstances, *i.e.*, where the interpretation does not agree with other diagnostic data or where there has been question regarding utilization of the full quota of dye, the intravenous test should be made. A second peroral test after a week's interval may be of service if the intravenous is not available.

In this comparison a corollary worth mentioning was the demonstration in 1 case of the effect of passive congestion of the liver on the value of the tests. A mildly congested liver led to "absent shadow" reports in an ambulant patient both by peroral and intravenous methods. With suitable rest and digitalis therapy, a repeat peroral test was made and perfectly normal gall bladder function reported. Nothing in the history or subsequent course of several months has led us to suspect gall bladder disease in this particular patient. A liver which cannot adequately secrete the dye will, it must be remembered, give the same cholecystographic result as a gall bladder which cannot receive or concentrate the dye.

Conclusions. The peroral cholecystogram with the present technique has certain inescapable disadvantages, indicated by the fact that one-third of the tests in the present series led to uncertainty in interpretations or disagreed with the assembled clinical and laboratory data. On the other hand, this method is free of the chief drawbacks of the more accurate intravenous technique, namely, difficulty in administration and untoward reactions. It is justified as the single test of gall bladder function, however, only if its limitations in the mild or early case are appreciated by the clinician.

The intravenous technique may not be used casually or haphazardly. Its reactions, however, are not such as to preclude its use for office or dispensary patients.

The procedure suggested is that the peroral test be used routinely, to be checked in case of doubt by the intravenous. The intravenous injections should be made by a member of the clinical staff, experienced in the technique, at a fixed station where proper equipment is concentrated.

NOTE.—We desire here to express our gratitude to Miss Ethel M. Showers for her very valuable technical assistance.

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THE PATHOGENESIS OF PERIGASTRIC ABSCESS COMPLICATING PEPTIC ULCER.

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Ever since the subject of gastroduodenal ulcer has been intensively studied, the view has been held that perigastric abscess complicating peptic ulcer is the result of slow gradual perforation of the gastroduodenal wall. Brunner,[1] in his classical report on perforated ulcer published in 1903 indicated the current surgical opinion regarding perigastric abscess* in the following introductory statement: "My exposition is limited to ulcers which perforate suddenly into the free abdominal cavity to the exclusion of those which perforate either slowly or in the walled-off space resulting from preformed adhesions. The clinical picture in the latter cases is an essentially different one involving, as a rule, a more chronic affection which leads to delimited peritonitic, mainly subphrenic abscesses, the surgical management of which consists for the most part in simple incision." Up to the present time the view expressed by Brunner has remained practically unmolested, although experience with peptic ulcer and its complications has increased enormously. Moynihan,[2] who is rightfully considered one of the greatest surgical authorities on digestive ulcer, shares essentially the same opinion as Brunner. Moynihan separates perforation of ulcer into three varieties, *viz.*, acute, subacute and chronic. Regarding the latter, he states, "In chronic perforation the ulcer has slowly eaten its way through the stomach coats, and a protective peritonitis has had time to develop at the base. The escape of the stomach contents is, therefore, merely local; barriers of lymph confine the fluid to a restricted area and a perigastric abscess forms."

The internist, who has a better opportunity than the surgeon of observing the ulcer patient from the very start shares the identical view with regard to the genesis of a complicating abscess. The most

* For the sake of convenience the term perigastric abscess is often used in connection with perforated peptic ulcer to apply to collections of pus not only in the immediate gastroduodenal region but also in more remote sites, particularly the subphrenic spaces. Wherever mentioned in this paper, perigastric abscess has the above broad connotation unless otherwise specified.

representative medical opinions can be obtained, perhaps, from the latest works on diseases of the stomach. Rehfuss,[3] after concluding his discussion on acute perforation, introduces the subject of perigastric abscess with the following paragraph: "Less dramatic in its intensity, but nevertheless accompanied by considerable gravity, is the formation of a subacute perforation followed by abscess formation. These patients usually present a history of months or years of chronic indigestion of the ulcerous type, obviously becoming more acute and more persistent. Sooner or later they are completely incapacitated by their pain and there is unquestioned evidence of a slow perforation. This is followed not by general perforation, but either by localized abscess formation or by the formation of dense adhesions and a fistulous tract into one of the adjacent organs, more particularly the liver or the pancreas." In connection with the consideration of the pathologic anatomy of ulcer complications Crohn[4] speaks of "cases in which the perforation is a slow process (chronic perforation) with resultant limiting adhesions or local abscess formation." Similar opinions are found in almost all medical and surgical texts, a dissenting view such as expressed by Walton[5] being quite exceptional.

In our clinical work at the Cook County Hospital with ulcer and its complications we had the opportunity of following from the earliest stages 8 patients who presented the final picture of "chronic perforation with perigastric abscess." In all of the patients observed the symptoms of onset were almost unmistakably those of acute perforation. In fact, a movable gas bubble, which is practically pathognomonic of rupture into the free abdominal cavity (Vaughan and Singer)[6] was demonstrated roentgenologically in 5. Operation was not performed at the time of admission in the 8 cases because permission was not granted or the attending surgeon was in doubt as to the diagnosis. Our experience in these few instances of abscess following acute perforation led us to question the accepted frequency of chronic perforation as a cause of intraäbdominal suppuration. We therefore undertook to investigate the incidence of acute and chronic perforation in cases which proved ultimately to be instances of perigastric abscess complicating peptic ulcer.

Through the courtesy and coöperation of our colleagues on the attending and resident staffs we were able to study, within the past 4 years, 22 additional patients with perigastric abscess of ulcer origin. Five were observed shortly after the acute perforation and for one reason or another were not operated upon but were allowed to progress to abscess formation. The remaining 17, when first admitted, complained of vague abdominal symptoms which were subsequently proved to be due to localized abdominal suppuration of ulcer genesis. In approximately two-thirds of the cases entering the hospital during the abscess stage, no mention of antecedent acute pain was made in the history. In these cases a sub-

acute or chronic perforation was assumed. By pertinent questioning with particular reference to the occurrence of previous violent pain which the patient failed to mention or to associate with the present illness, we succeeded without difficulty in obtaining a classical description of a previous acute perforation from 16 of the 17 patients. In each of these 16 cases the moment of rupture could be definitely and precisely established by the history. In the 1 remaining case an intolerable, overwhelming pain suggestive of perforation was not elicited. Of 30 cases, therefore, of perigastric abscess of ulcer origin evidence of acute rupture was obtained in 29, leaving only 1 in which a chronic or silent perforation may be assumed.

The present belief that perigastric abscess generally follows chronic perforation is based upon an incomplete knowledge of the natural history of ruptured ulcer. It is generally assumed that ulcers which, perforating acutely, not closed surgically, remain patent indefinitely and usually lead to death. In a small percentage of cases, according to current belief, recovery may occur, but only after a stormy and prolonged convalescence. While it is true that a rapidly fatal illness occurs in a certain proportion of unoperated cases, the course and outcome is by no means a uniform one. In an equal or possibly greater proportion of cases the original perforation, instead of remaining patent, becomes spontaneously closed and ceases to discharge material into the peritoneal cavity (Singer).[7] In such cases the postperforative course does not conform to the classical case with unlimited leakage, but varies with the amount and character of the escaped gastroduodenal content. In that group of cases where spontaneous closure occurs rather late and the quantity of material extravasated is relatively large the resultant peritonitis is likely to be a severe one. If the patient survives, the diffuse peritoneal inflammation, after producing stormy manifestations, becomes focal and one or more localized collections of pus are likely to remain. Subsequent absorption, spontaneous or surgical evacuation, or extension of the inflammation may occur. In a second group in which the perforation is sealed earlier and the amount of efflux is considerably less, the ensuing peritonitis is likely to be of only moderate intensity. The more or less diffuse peritoneal inflammation runs a short and relatively benign course, lasting usually several days. After this time, unless absorption is complete, signs of abscess generally appear. In a third group of acute perforations with spontaneous closure the leakage is only slight and trifling in amount and the symptoms of peritonitis are mainly local and transient. In these cases which correspond to the *formes frustes* type of Singer and Vaughan[8] the postperforative symptoms are surprisingly mild and frequently disappear within less than 24 hours, although a residuum of infectious material may remain. Failure to recognize the fact that walling-off of a perigastric abscess occurs *after* acute rupture has taken place, explains in a great

measure perpetuation of the view of chronic perforation with slow leakage.

Another reason why the conception of chronic perforation prevails, is failure to inquire into the illness which generally antedates the symptoms referable to the perigastric abscess. Between the time of recovery from the immediate effects of the acute perforation and the development of the abscess there is frequently an intervening period during which the patient may feel comparatively well. If chronic perforation is assumed to exist and the history of onset is not volunteered the acute pain of perforation will be overlooked. Even in those cases where the extravasation is rather copious a noteworthy improvement may occur before symptoms and signs of abscess supervene. In Case 1, for instance, the patient, following a severe diffuse peritonitis, was restored to fair health and was ambulatory for a time before manifest symptoms of abscess appeared. In the cases with moderate escape of gastroduodenal content it is the rule to observe a decided improvement in the patient's condition before the abscess asserts itself clinically. After the peritonitis of onset has receded and the patient has felt comparatively well for a few days and perhaps ceased to remain confined, symptoms of abscess are likely to supervene and force the patient to return to bed. Here, as in the previous group, there may be a latent period of days, weeks or months following apparent recovery from the perforation before the abscess makes its presence felt. During this time the patient's health is likely to be somewhat impaired, although no local symptoms or signs are noted. In those cases with minimal leakage an abscess, if it occurs, manifests itself, as a rule, after the patient has to all appearances completely recovered from the perforation. The brief and tranquil illness immediately subsequent to the acute rupture is usually followed by a variable period of good health, during which time the patient is able to carry on his former occupation. When the abscess begins to evidence itself, the incident of the perforation and its immediate effects are no longer fresh in the mind of the patient and the two illnesses generally are not associated. It is necessary, in this group particularly, to obtain a minute-by-minute history if the onset of the acute, sudden, violent pain of perforation is to be elicited.

That chronic, silent perforation does occur cannot be denied. A localized phlegmonous gastritis at the base of an ulcer may extend to the peritoneum, as suggested by Payr,[9] and lead to the insidious development of an intraperitoneal suppurative process. However, the presence of a phlegmon in association with a peptic ulcer is extremely rare. A second and more likely occurrence is that bacteria may, with relative silence traverse the thin, unruptured base of an ulcer as described by Guibal[10] and von Bergmann.[11] Here, however, the escape of organisms is relatively slow and the peritoneum is well able to protect itself against invasions of this type in all but

the exceptional case. The development of a purulent peritonitis proceeding from an ulcer with an intact base can be considered a rare event. For practical purposes the pathogenesis of perigastric abscess complicating ulcer other than acute perforation can be disregarded.

A correct conception of the relationship of perforation of an ulcer to perigastric abscess is of both diagnostic and therapeutic importance. We consider the knowledge that intraäbdominal abscess results from acute rather than chronic perforation necessary for the early recognition and intelligent treatment of many cases of perigastric abscess. For diagnostic purposes the concept of chronic perforation is valueless and often misleading. It assumes that the solution of continuity of the gastric or duodenal wall occurs so slowly and silently that the actual time of rupture cannot be determined. The earliest evidence of perforation, according to this view, is the presence of a clinically recognizable abscess. In other words, the diagnosis of an abscess is required before a perforation can be suspected. The notion of acute perforation here elaborated makes the diagnosis of perigastric abscess possible during its incipiency. A history of sudden, violent pain having the well-known characteristics of a perforation, followed later by vague abdominal complaints and when sought for, a slight rise in temperature is sufficient to direct attention to the probable presence of a perigastric abscess. The value of the acute perforation doctrine in diagnosis and therapeusis is well examplified in the appended case reports dealing with intraäbdominal suppuration of ulcer origin.

Case Reports. CASE 1.—F. C., a man aged 55 years, entered the Cook County Hospital on June 14, 1929. The history obtained at that time and recorded on the chart was that 38 hours before admission the patient, while walking in the street, experienced an epigastric pain which increased rapidly in intensity and caused him to return home and take to bed. After 24 hours the pain began to diminish in intensity but did not subside completely. He vomited several times the day after onset following attempts at drinking. No bowel movement occurred since onset. No history of previous similar attacks or of any gastrointestinal symptoms other than constipation was elicited. The remaining history was essentially negative except for the presence of a chancre in 1899.

The physical examination disclosed a well-developed colored male, rather acutely ill. The temperature was 100° F., the pulse 64, and the respiratory rate 18. The blood pressure was 144 systolic and 68 diastolic. The significant observations consisted of the following: The pupils reacted sluggishly to light; the heart was irregular and the tones somewhat distant and weak. The abdomen was rigid, particularly in the right upper quadrant. Moderate tenderness corresponding to the extent of the rigidity was elicited. The liver dulness was not obliterated. The knee jerks were sluggish. In the urine a 4+ reaction for albumin was obtained and numerous casts were seen in the sediment. The white blood count was 10,550. The diagnostic considerations included a coronary occlusion or dissecting aortic aneurysm and an acute abdominal condition due to mesenteric embolism, ruptured ulcer or perforative appendicitis. Owing to the obscurity of the diagnosis the attending surgeons decided that operation was not indicated.

FIG. 1.—Case 2. Roentgenogram taken, March 13, 1930, 15 days after acute pain of ulcer perforation. Beneath the right diaphragmatic dome is a fluid level (subphrenic gas-containing abscess) indicated by arrow. The opacity at the base of the right chest is due to fluid.

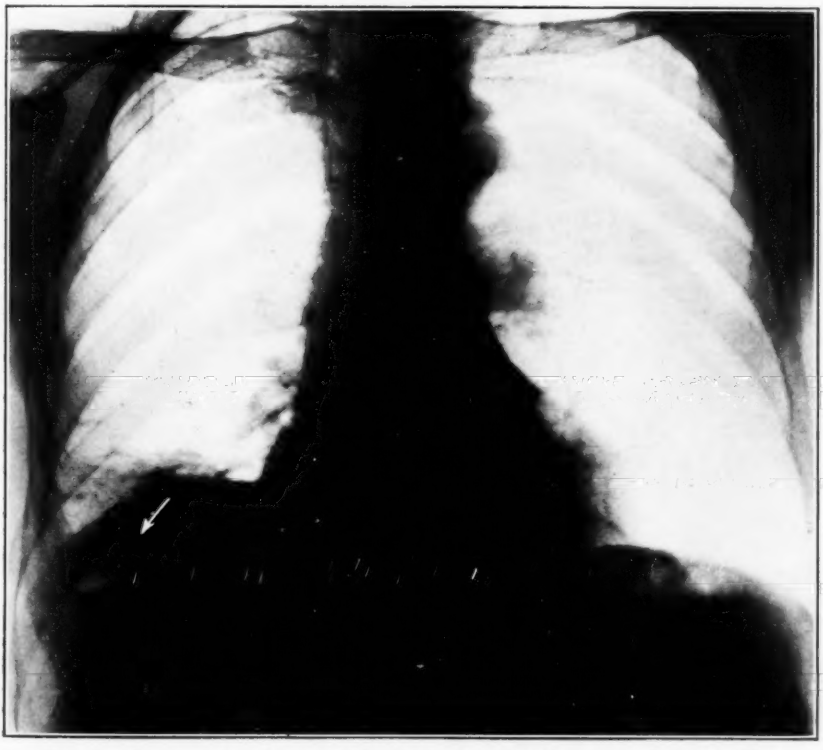

FIG. 2.—Case 2. Appearance of film of March 15, 1930, taken 2 days after Fig. 1 and 17 days after perforation. The shadows produced by the subdiaphragmatic air (indicated by arrow) and the supradiaphragmatic fluid have decreased in size.

FIG. 3.—Case 2. Artificial pneumoperitoneum performed, April 28, 1930, resulting in the accumulation of air beneath the left dome. No air is seen to collect between the right leaf of the diaphragm and the dome of the liver indicating obliteration of the right subphrenic space.

The patient improved rapidly, and on June 16, 1929, 2 days after entrance, it was recorded the patient felt well and that the temperature did not rise above 99.4° F. Ten days after admission, a firm, smooth mass was palpated in the right subhepatic region. The thought of a kidney tumor as the cause of the symptoms suggested itself and cystoscopic examination was advised. Pyelography failed to show any abnormality of the right renal pelvis. The surgeons were unable to arrive at a satisfactory conclusion and transferred the patient to the medical service 2 weeks after admission for diagnostic study. While in the medical ward the subhepatic mass disappeared, the patient became afebrile and the pulse assumed a regular rhythm. Various types of examination were resorted to but none seemed to throw any light upon the origin of the patient's symptoms. He was discharged in apparently good health on August 3, 1929.

Two weeks following his discharge the patient was readmitted to the hospital on account of pain in the upper abdomen which appeared rather suddenly 5 days after he returned home. It was somewhat sharp at the onset but gradually diminished to a mild pain which persisted. A few days after the onset of the pain the patient perceived an egg-sized, firm mass in the left upper quadrant which had progressively increased in size. The temperature, pulse and respiratory rates were normal. The contour of the abdomen was distorted by the prominence of a mass in the left hypochondrium which was the size of an orange, tender and slightly mobile with respiration. A tentative diagnosis of carcinoma of the transverse colon was made. A barium enema disclosed no abnormality of the colon.

At this juncture we had occasion to interview the patient regarding his past and present illness. By painstaking and persistent questioning we obtained the following significant history: For many years the patient has suffered from mild epigastric distress which he ascribed to constipation and which, when analyzed, had the characteristic rhythmic relation to meals and the seasonal periodicity of ulcer pain. During the 3 days preceding the onset of acute pain which occurred prior to his first entrance, the patient experienced an augmentation of his previous epigastric distress and suffered also from night pain and vomiting. On June 12, 1929, at about 7 P.M., following a day of considerable discomfort and almost complete abstinence from food on that account, the patient was suddenly seized within a half block of his house by a severe epigastric pain. He stooped forward, and with his arms crossed over his abdomen he succeeded, after much effort, in arriving home. By this time the pain had reached its acme and was exceedingly violent and acute. The patient flung himself onto his bed and writhed about in an attempt to find a comfortable position. A physician who was summoned arrived within a hour of onset and administered a hypodermic which rendered the pain less intense but did not entirely alleviate the patient's suffering. A second hypodermic was required a little later, and after 24 hours the pain moderated sufficiently to permit the patient to rest.

After obtaining the above history and reflecting on the physical signs noted at the time of the initial admission we inferred that the patient had probably suffered an acute perforation of a chronic ulcer. A review of the history indicated that the symptoms and signs recorded during his first period of hospitalization were quite characteristic of the postperforative stage of a ruptured ulcer which had been spontaneously sealed. The subhepatic mass which appeared and later disappeared we assumed to be a collection of gastroduodenal content and purulent exudate which was absorbed or spontaneously evacuated. After reaching the conclusion that a

previous rupture had occurred, it was a simple matter to associate the tender mass which recently appeared with the antecedent history. A diagnosis of perigastric abscess was therefore made and operation advised. Our colleagues were still somewhat hesitant in accepting our opinion, and on August 30, 1929, a Roentgen ray examination of the stomach was ordered and the following report rendered: "The right diaphragm is abnormally high and relatively fixed. There is a deformity of the bulb characteristic of ulcer." On September 3, 1929, approximately 12 weeks after perforation, laparotomy was performed and a perigastric abscess was found and drained. The patient made an uneventful recovery and was discharged September 19, 1929. Up to the present date he has had no further difficulty, except at times when he becomes lax with his diet and medication.

CASE 2.—M. M., a well-preserved man, aged 66 years, admitted to the medical service on March 11, 1930, complained of belching and epigastric pain of 2 weeks' duration. In the hospital record his history, as obtained by the junior intern, reads as follows: "The patient felt perfectly well until 2 weeks ago, when he suffered from severe cramp-like abdominal pain which lasted for a day or so and then gradually subsided. Vomiting, which occurred for the first time 2 days after the onset of pain, was repeated 2 or 3 times daily since, but ceased 24 hours preceding admission. There has been no relationship of the vomiting to the quality or quantity of food eaten. During the first few days of his illness hiccough was a prominent symptom but has now completely disappeared. For the past two years there has been dyspnea on exertion, which became aggravated recently and associated with cough and expectoration especially upon change of position."

The temperature upon entrance was 99.2° F.; the pulse rate, 76, and the respiratory rate, 20. The blood pressure was 120 systolic and 72 diastolic. The physical observations were those of an insufficiency of the mitral valve, effusion in the right chest, a tender, palpable liver and a slight edema of the ankles. A diagnosis of right pleurisy with effusion probably tuberculous and an independent myofibrosis with a relative mitral insufficiency was made. Later it was attempted to explain the entire picture on the basis of a decompensated heart until thoracentesis was resorted to and yielded 400 cc. of a clear fluid having the characteristics of an exudate. Vomiting recurred 2 or 3 times daily while the patient was under surveillance. One of the attending physicians being apprized of the emesis succeeded in obtaining the additional history of postprandial distress and diagnosed a peptic ulcer in addition to a right pleural effusion. A relationship between the two was considered but thought unlikely. An Ewald test meal on March 12, 1930, yielded 250 cc. with 67 degrees free and 85 degrees combined acidity.

At this point in the course of observation we had the opportunity of questioning and examining the patient. We elicited the story that for 15 years he had suffered periodically from epigastric distress which was typical of peptic ulcer. He had consulted no physician, as he could always obtain practically instantaneous relief from baking soda, which he used in large amounts. Prior to the onset of acute pain he noted no unusual deviation from his chronic ulcer distress and no symptoms which might have been considered prodromes of a perforation. On February 26, 1930, at 6 P.M., while reclining on account of languor, the patient was suddenly seized by violent abdominal pain which began on the right side but within a few minutes became generalized. The patient broke out in a cold sweat and began to writhe about in agony. His abdomen, which he attempted to

protect with his hands, became as "hard as iron." He called to his wife and implored her between gasps to telephone for a physician immediately. During the 30 minutes that elapsed between the time the physician was summoned and his arrival the patient suffered from intolerable pain which he believed he could not have endured much longer. A hypodermic was immediately administered, following which the patient's suffering was somewhat relieved. The pain gradually diminished in intensity and by the following day it was relatively mild. Hiccough was first noted the day after onset and subsided readily to recur for short periods at intervals of a day or so. Four days after onset the patient first began to vomit. Shortly before entrance both the pain and emesis completely subsided. The reason the patient came to the hospital at this time was mainly on account of debility and shortness of breath.

Based upon the history which indicated a recent perforation with diaphragmatic irritation (hiccoughing), the evidence of fluid in the right chest, the depressed liver and a subfebrile temperature, the diagnosis of subphrenic abscess with pleural extension was made. Our diagnosis was questioned until Roentgen ray examination (Fig. 1) undertaken on March 13, 1930, showed a high right diaphragm above which was radiographic evidence of fluid and below which was fluid and air. A barium meal disclosed the presence of a prepyloric deformity which caused 90 per cent retention at the end of 6 hours. The evidence of an ulcer and of a subphrenic abscess was therefore conclusive. The history pointed almost unmistakably to a direct relationship between the two affections. On account of the spontaneous improvement operation was not urged. A modified Sippy treatment for ulcer including bed rest was instituted. The temperature gradually dropped, the vomiting ceased and the abdominal pain subsided. Subsequent Roentgen ray examinations (Fig. 2) showed a progressive decrease in the supra- and infradiaphragmatic shadows, both of which disappeared by April 4, 1930. The diaphragm on this day showed a normal mobility, the prepyloric deformity persisted, but no retention of the 6-hour barium meal occurred. The patient left the hospital April 11, 1930, feeling quite well. He returned to the follow-up clinic complaining of shortness of breath and was advised to reënter the hospital for cardiac management. On rest and digitalis his heart symptoms vanished. Before final discharge of the patient it was decided to investigate the relationship between the superior surface of the liver and the right dome of the diaphragm. For the determination of the presence of subphrenic adhesions, artificial pneumoperitoneum was resorted to (Fig. 3). In no position was it possible to cause air to enter the right subphrenic space, which was assumed, therefore, to be obliterated as a result of organization of the previous exudate.

Summary and Conclusions. 1. In a series of 30 cases of perigastric (including subphrenic) abscess of ulcer origin, convincing evidence of a previous acute perforation into the free abdominal cavity was obtained in 29.

2. The formation of adhesions which are found about a perigastric abscess generally follows rather than precedes perforation.

3. Between the time of recovery from the acute symptoms of perforation and the time of onset of manifestations of a perigastric abscess a period of fair health frequently intervenes. It is on this account that a patient often fails to associate the two illnesses.

4. Unless a previous acute perforation is suspected and a minute-by-minute history of the initial symptoms obtained, the antecedent occurrence of a sudden, violent abdominal pain is often not elicited.

5. In most instances a perigastric abscess of ulcer origin represents a neglected opportunity on the part of the patient, but perhaps more frequently on the part of the physician.

6. Early recognition of perforated peptic ulcer, especially the type with mild postperforative symptoms (*forme fruste*), together with timely operation will eliminate the greater number of perigastric abscesses.

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INSULIN AND APPETITE. I. A METHOD FOR INCREASING WEIGHT IN THIN PATIENTS.

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It is not generally appreciated that insulin plays an important rôle in the hunger-producing mechanism. As far back as 1924 Harris described 3 cases of hyperinsulinism in which the patients

suffered insatiable hunger, and he suggested that insulin was closely associated with the hunger mechanism. Bulatao and Carlson have injected insulin in normal fasting dogs and obtained increased gastric motility, an activity which was readily inhibited by injecting dextrose. A similar experiment was performed on human subjects by Quigley, Johnson and Solomon. They injected 12 to 20 units subcutaneously in normal fasting men and demonstrated that marked sensations of hunger accompanied the increased gastric motility. These phenomena, too, could be readily inhibited by introducing dextrose into the duodenum.

This simple yet effective method of increasing the appetite is seldom employed clinically. In the few case reports concerned with this treatment, the results have been gratifying in large measure. Falta, in 1925, reported the results in 3 abnormally thin patients to whom he had administered insulin as a stimulant to the appetite. Two had suffered with a chronic infection of the throat, while the third was thin but otherwise normal. In each case the state of nutrition was poor and the resistance to disease inadequate. The appetite was small and the caloric intake was low. Falta employed injections of 10 to 15 units of insulin every 3 hours and furnished large amounts of food at all times. The patients quickly developed wellnigh insatiable appetites, consumed greatly increased quantities of food and gained from 10 to 20 pounds in 20 to 40 days. In one case, the appetite was increased so markedly as to closely resemble bulimia.

The number of thin patients who are otherwise normal is considerable. Out of the last 100 private patients who consulted one of us, 4 were in this category. Add to this number the patients convalescing from prolonged illnesses, and the large population in state institutions who stop eating because of mental depression and anxiety states, and the total becomes even more considerable. The appetite in most of these patients is not large and in some cases excessively small, so that the caloric intake is insufficient to maintain the nutritional state adequately. Most of them have resorted to the usual tonics and stomach bitters without any benefit and have finally accepted their reduced physical proportions and poor cosmetic effect with hopelessness and resignation. In this type of patient insulin quickly converts a meager appetite into a large one and the food intake is increased proportionately.

The Method. The treatment is begun by administering 3 units of insulin subcutaneously every 3 hours. In order to avoid an insulin reaction, patients are urged to eat liberally ½ hour to ¾ of an hour after the injection. The dose of insulin is gradually increased until 10 units or even larger doses are injected every 3 hours. The patients are further acquainted with the nature of an insulin reaction and are urged at all times to have available carbohydrates in case an urgent need for it arises. The following cases are striking in their

improvement and illustrate clearly the ease of the method and the absence of untoward incidents during the treatment:

Case Reports.—Case 1. M. T., female, unmarried, aged 33 years, housekeeper, F. H. and P. H. not significant, has always been highstrung and worrisome. Six months ago an episode in the home greatly upset her. Since then though the facts and situation have been almost forgotten, her appetite has grown meager and her weight dropped steadily from 130 pounds to 100 pounds. She could not eat much, was quickly satisfied and felt full after ingesting a small meal. She has grown sensitive about her looks and has therefore avoided her friends. Furthermore, she was fearful about the possibility of having tuberculosis. Her menstrual history was normal. The physical examination revealed nothing of note except that she was thin, weighing only 100 pounds though 5 feet 5½ inches tall. For 3 weeks she was given relaxing packs and tonics, a complete rest from home duties and a change of environment. Three weeks later she weighed 102½ pounds. She was then placed on an insulin régime. On the third day, the patient was awakened during the night suffering from weakness and sweating and all signs of an insulin reaction, and occasionally a similar weak feeling was experienced just before the evening meal. The gain in weight was very rapid. In 3 days she weighed 105½ pounds; in 7 days, 108½ pounds; in 14 days, 115 pounds; in 21 days, 119½ pounds; in 28 days, 125 pounds. Her cheeks became rounded and her figure improved. She regained confidence in herself and returned to her former social life. Three months later her weight was unchanged and she seemed normal in every respect.

Case 2.—H. Q., female, aged 24 years, height 5 feet 7½ inches, weight 108½ pounds, has always felt well. Her immediate relatives are living and well nourished. Four years ago she had acne of the face which left it somewhat scarred, since then her weight has gradually fallen from 130 pounds to 108½ pounds. Her appetite seemed good and she claimed to eat well, but her weight remained consistently low. She was of a nervous temperament, worrisome and always accepted other peoples' burdens. The treatment was started with 5 units every 3 hours. After the first injection there was created great relish, and for the first time she really enjoyed her meals. The food intake rose rapidly and 3 days later the weight was 110¾ pounds. At this time the insulin was raised to 10 units every 3 hours. Three days after the dose was increased her weight was 112¾ pounds, 5 days later 118½ pounds, so that in 12 days the weight had increased 10 pounds. The following is a characteristic day's food intake for this patient:

Breakfast: 2 oranges, 2 slices of buttered-toast, 1 egg and a glass of milk.

At 10.30 A.M.: Two frosted cupcakes and a glass of milk.

At 1.00 P.M.: A large salmon salad, a whole heart of lettuce, 2 heaping tablespoons of mayonnaise, 1 egg, 2 rolls, 2 cubes of butter, 2 slices tomatoes and 2 olives, a Bisque Tortoni and a glass of milk.

At 3.00 P.M.: A Hershey chocolate bar.

At 6.00 P.M.: Six oysters, a plate of tomato soup, a quarter of a chicken, 2 baked potatoes with a tablespoon of butter, a helping of spinach, 5 tablespoons of fruit jello, 3 slices of bread and 3 tablespoons of butter, 6 chocolate cookies and a glass of milk.

It is not difficult to appreciate why there was a rapid gain in weight following the intake of such a quantity of food. The insulin was then discontinued and the weight remained at 118½ pounds for a month.

Case 3.—A. S., female, aged 20 years, married 1 year, complains chiefly of nervousness, weakness, loss of appetite, and loss of weight during several months. At this time she consulted a physician for pain and stiffness in her knees. She was told she had rheumatism and warned of possible heart disease to follow. Although her pains were fleeting, she continued to brood

and worry because of her heart, lost appetite and began to lose weight. Examination revealed no abnormalities; her height was 5 feet 6 inches; weight, 112½ pounds. This patient was started with 5 units of insulin given every 3 hours for 18 days, and then experienced for the first time real pleasure in her eating. There were several instances during the treatment when mild insulin reactions occurred. These, however, were finally eliminated by increasing the food following each injection. The weight rose to 115½ pounds in 3 days. In 6 days, it was 116½ pounds; in 8 days, 117½ pounds; in 10 days, 118½ pounds; in 12 days, 120¼ pounds; in 18 days, it had only risen to 121 pounds. At this point the insulin was raised to 7 units every 3 hours. The weight did not improve but instead moderate insulin reactions of weakness, sweating and faintness occurred after the afternoon dose and also at night. Accordingly the dose was reduced to 5 units and the food intake was increased after the afternoon and night dose. Five days after this change the weight was 125 pounds. The insulin was then discontinued, but the weight has remained at 125 pounds for 1 month.

Case 4.—T. N., female, aged 26 years; height, 5 feet 7½ inches; weight, 110 pounds. Apparently well and in good health but thin and desiring to improve her weight and thereby her appearance. She was endowed with but a frail appetite which was quickly satisfied. She was started on 3 units every 3 hours, November 10, 1930. At this time the weight was 112 pounds. On the 18th, the weight was 118.6 pounds, and the dose was increased to 10 units ever 3 hours. The weight steadily rose until December 9, when it was 126.6 pounds. At this time insulin was discontinued because of an intercurrent grippe. December 15, the weight had fallen to 122 pounds and insulin was resumed to 10 units every 3 hours. On the 17th, the weight rose to 124 pounds, and on the 19th it was 125 pounds. The insulin was then discontinued and the weight 6 months later was 121 pounds although she had just recovered from an intercurrent illness of 2 weeks' standing.

Discussion. The rapidity with which the appetite is restored and the quantity of food intake is increased is thus well illustrated in Cases 1 and 3. The first patient gained 22½ pounds in 28 days, the second gained 10 pounds in 12 days, the third gained 12½ pounds in 23 days and the fourth gained 15 pounds in 39 days. The untoward insulin reactions were surprisingly small when one considers that 45 to 65 units of insulin were administered daily to normal persons.

The question has been raised as to whether the rapid weight increase is due to water retention. This is hardly likely as the caloric intake was doubled and tripled during the treatment. Furthermore, the gain in weight remained for the most part after the insulin was stopped. Temporary water storage under insulin treatment should be rapidly eliminated when this hormone is discontinued, and the weight should revert quickly to the former level. This did not occur in these patients. Falta tested this possibility further on his patients by administering large doses of diuretics but failed to produce increased water elimination and loss of weight. He also concludes that water storage is not an appreciable factor in the rapid improvement in weight under insulin administration.

On the other hand, there is sufficient evidence that insulin does promote fat deposition. It has been known for years that rabbits employed for the assay of insulin gain weight rapidly the first few

weeks. It is also well known that depancreatized dogs when treated with proper amounts of insulin and diet can be made to gain weight rapidly. It is of course well known that most diabetic patients who are on a liberal diet with sufficient amounts of insulin gain weight rapidly. The rapid gain in weight of the cases above described, therefore, are more likely due to fat deposition. Furthermore, it has been shown that insulin causes a decrease in blood fat, apparently due to storage.[7]

It is remarkable to compare the amounts of food taken before treatment with what was ingested during the treatment. A. S. was satisfied with tea and one-half a slice of toast for breakfast, but after 10 units of insulin took a glass of orange juice, a bowl of oatmeal with sugar and cream, 2 rolls and butter, 2 eggs, and a glass of milk. All this she ate with real pleasure and gusto. Ingestion of such an amount of food before she took insulin would have been impossible and might even have nauseated her. It seems as if the capacity of the stomach was considerably increased after the insulin injections. It is quite probable that the size of the stomach plays an important rôle in determining the amount of food which can be taken with pleasure. It is well known that after chronic starvation, one can take but very small amounts of food and that only after several days does the capacity of the stomach become normal.

The physiology which underlies the pleasure of eating is still obscure. The patients of this series had clearly lost the zest obtained from food, before treatment was begun. Eating was more a habit than a pleasure, something to be despatched with rapidity as a necessity of life. Following the administration of insulin, however, a feeling of pleasure appeared and as the dose was increased so was the joy of eating. Patient 3, who was nauseated by the sight of food before treatment, developed a ravenous appetite, and following insulin administration ingested large quantities of food with relish. Thus, insulin not only creates hunger, but also generates the pleasure which is associated with its satisfaction.

It has long been known that patients subjected to worry and anxiety quickly lose the appetite and grow thin. That the mind may mediate these effects through the insulin mechanism, gains support from recent work. Beattie, Brow and Long (1930) have traced anatomic pathways from the hypothalamus to the sympathetic fibers in the cord and have thus established a direct connection between the brain and the sympathetic nervous system. Stimulation of this region of the brain will cause a rise in blood pressure and a discharge of adrenalin from the adrenal glands. It is now known that adrenalin tends to inhibit insulin activity[3, 4] while the sympathetic fibers paralyze gastrointestinal motility. It is also conceivable that the sympathetic nerves may cause an inhibition of insulin formation by a direct action on the pancreatic cells. It

is therefore not difficult to understand how emotional states can, through the sympathetic nervous system, interfere with the insulin mechanism and so diminish the appetite.

Summary and Conclusions. 1. Four patients are reported who gained weight rapidly following the administration of insulin. As a result of the treatment, there was a great increase in the appetite, probably a considerable enlargement of the stomach capacity and the generation of great pleasure associated with eating.

2. The gain in weight is not due to water retention, but rather to actual tissue accretion.

3. The relation of mental states to anorexia is considered, and their influence upon the insulin mechanism is traced.

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METABOLIC CHANGES AND TREATMENT OF OBESITY.*

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The attention of every physician is directed sooner or later to the question of obesity; not only because of the desire of some patients to reduce for esthetic reasons, but because in obesity there are real inherent dangers. The susceptibility of the obese person to infectious disease, especially pneumonia, to diabetes and to the degenerative diseases of heart and bloodvessels is sufficient ground for our interest in the subject. It is my object at present to discuss some phases of obesity, which although not new, yet are of sufficient importance to be worthy of review, and to describe the rôle that dehydration may play in the therapy of some forms of obesity.

Obesity is usually classified as that of exogenous or of endogenous character. By exogenous is implied that the person becomes obese because he eats too much or exercises too little; in other words the principle of conservation of energy is operative in this type of obesity. DuBois[1] aptly said, "We do not yet know why certain

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individuals grow fat. Perhaps it would be more accurate to say that we do not know why all the individuals in this overnourished community do not grow fat." It is apparent then, and it is generally admitted by students of obesity that there are some persons in whom there are some additional factors besides the excess of food or insufficient muscular exercise which would tend to account for the tendency to become obese. We refer to the so-called endogenous type of obesity. In practice it is frequently difficult to know where exogenous obesity ends and endogenous begins. In the person who has a tendency to become obese there must be some disturbance of the mechanism which enables another person to burn an excess of food and to retain his stationary weight.

Some of the obese patients have an excessive desire for food, and by attempting to reduce their caloric intake they may suffer from weakness, fatigue, headache and dizziness, and nervousness and yet fail to lose weight. It is this type of obesity that constitutes the problem in the management of the disease.

In concerning ourselves with obesity we must consider the total metabolism of the individual, that is, his or her basal metabolism, the effect of exercise on oxygen consumption, the stimulation in metabolism that follows the ingestion of food, that is the specific dynamic action of food. Water and salt metabolism are also of importance and in some patients appear to play a prime rôle in the gain or the loss of weight.

Basal Metabolism. Out of 21 patients who were under our observation within the last 12 months, only 2 patients had a perceptibly minus basal metabolic rate. One patient (No. 1) was a boy, aged 13 years, who had dystrophia adiposogenitalis and whose basal rate was minus 30; the other was a woman, aged 47 years (No. 20) who had a thyroövarian obesity, whose basal rate varied between minus 20 and minus 30, average minus 25, on two different occasions. The third patient (No. 12) in whom the basal rate markedly deviated from the normal and whom we shall discuss again later, was that of a man, aged 38 years, with cerebral obesity; he had a basal rate of plus 30. Patient No. 3 had a basal of plus 47. This patient developed thyrotoxicosis after she commenced to put on weight. All the other patients showed basal metabolic rates within the range of normality. This is in accordance with the experience of most clinics.[2,3] The conception of van Noorden that mild forms of hypothyroidism lead to obesity is, therefore, not borne out by facts.[4]

I recently studied a group of patients with hypothyroidism, all of whom had a minus basal metabolic rate.[5] Four out of 7 of these patients were underweight rather than overweight.

Different individuals respond variously to thyroid gland administration. According to Falta[6] the administration of thyroxin in some persons is followed by symptoms of thyrotoxicosis; on the other

hand the same amount of thyroxin in other persons remains ineffective. We often observe a similar occurrence in obese persons.

TABLE 1.—BASAL METABOLISM IN OBESITY.

Name	Sex.	Age, years.	Weight, pounds.	Height, inches.	Basal metabolic rate.
J. K.	M	13	199	60	−30
F. G.	F	16	131	63	−13
H. S.	F	17	158	65¾	+47
R. B.	F	17	159	63	− 9
M. G.	F	23	212	67	− 7
M. S.	F	25	235	61	+ 2
V. M.	F	26	182	64	+ 5
R. R.	F	26	189	63¼	−17
N. N.	M	26	193	65	− 2
H. C.	M	27	282	76	−10
A. C.	F	32	290	62½	+ 7
T. B.	M	38	290	67	+30
J. S.	M	38	172	66	+ 4
N. S.	F	38	155	58	−12
C. W.	M	38	237	70	+ 2
M. H.	F	41	204	61	−15
J. B.	F	42	250	67	+ 7
I. G.	M	42	332	64	− 5
C. R.	F	42	269	61	− 9
J. R.	F	47	170	66½	−25
N. T.	F	53	190½	59	− 2

One-half grain of desiccated thyroid gland three times a day was given to an obese patient; within 10 days she developed tachycardia, nervousness and an increased sense of body heat without having lost any perceptible weight. On the other hand I have at the present time under my care a patient who has been taking desiccated thyroid for a period of 2 years, commencing with 2 gr. daily and bringing it up to 10 gr. daily for 8 months, without any evidence of thyroid intoxication and without loss of weight. Then again there are patients who lose weight rather rapidly under small doses of thyroid. In this connection the work of Enderlen and Bohnenkamp[7] as mentioned by Falta is of interest. They have shown that dogs with resected sympathetic nerve remain refractory to thyroid administration, while the same dose of thyroxin produces extreme emaciation and death in the control animals. Clinically it is known that patients who suffer from certain diseases of the central nervous system, such as epilepsy and syphilis of the brain, are resistant to thyroid therapy.

One must conclude, therefore, that thyroid hypofunction and consequently a low basal rate is of no great moment in the pathogenesis of obesity.

The Specific Dynamic Action of Food. One would expect in obesity a low specific dynamic action of food. Some early workers like Plaut,[8] Rolly[9] and Liebesny[10] had demonstrated a diminished specific action in obesity. However, Lauter,[11] Bauer[12] and others have found figures that do not materially differ from the normal. Wang,

Strouse and Saunders[13] found that carbohydrate and fat has very little effect on the specific dynamic action; however, protein gives the greatest depression in the curve. Strang and McClugage[14] have recently found no great difference in the heat of reaction to food in either mild or severe grades of obesity as compared with normal persons; they deny an abnormality in specific dynamic action any rôle whatsoever in the initiation of obese states. Spencer and McClelan, using the Sage calorimeter, have obtained normal curves for the specific dynamic action in obese men and women.[15]

I have studied the specific dynamic action of food in 7 obese patients.

TABLE 2.—EFFECT OF INGESTION OF A MIXED MEAL ON HEAT PRODUCTION.

Name.	Age, years.	Weight, lbs.	Height, inches.	Basal rate.	Metabolic rate. 45 min. after meal.	Metabolic rate. 90 min. after meal.	Per cent difference from basal of patient. 45 min. after meal.	Per cent difference from basal of patient. 90 min. after meal.
J. K. . . .	13	199	60	−30	−30	−30	0	0
R. B. . . .	17	159	63	− 9	− 2	+ 5	7(+)	14(+)
T. B. . . .	38	290	67	+30	+20	+20	8(−)	8(−)
N. S. . . .	38	155	58	−12	−17	−10	6(−)	3(+)
C. W. . . .	38	237	70	+ 2	+ 5	+ 8	3(+)	7(+)
M. H. . . .	41	204	61	−15	+17	+25	38(+)	48(+)
L. G. . . .	42	332	64	− 5	+ 5	+ 2	10(+)	7(+)

The meal consisted of 100 gm. of meat, 200 cc. of bouillon, 30 gm. of butter, 100 gm. of bread and 3 gm. of salt. The readings were taken before the meal, 45 minutes and 1½ hours after the meal respectively. We obtained figures not markedly different from normal persons, with two exceptions: in one case of dystrophia adiposogenitalis, there was a total absence of specific dynamic action; in another case of thyroövarian obesity, the specific dynamic action was considerably increased over the basal rate. It is rather interesting to note that this patient was susceptible to thyroid therapy. One-half grain of desiccated thyroid gland three times a day for 10 days produced marked symptoms of thyrotoxicosis. In evaluating the specific dynamic action we must bear in mind that even in normal individuals it may vary from minus 1 per cent to plus 31 per cent.[16] According to Pollitzer and Stoltz[17] 25 per cent of normal individuals may show a diminished or complete absence of specific dynamic action.

Then again there are some patients who are extremely thin due to hypophyseal disturbance and also patients with diseased autonomic nervous system, such as Raynaud's disease or scleroderma, who also show low specific action of food. According to Plaut[18] the specific dynamic action is under the influence of the anterior pituitary lobe. It is then apparent that the specific dynamic action is of no great practical moment in obesity.

The effect of muscular work on oxygen consumption in obesity

does not vary greatly from the normal. During heavy work the obese may consume more oxygen than a normal individual. Credit is due to Bernhardt[19] for pointing out that after light muscular work, 20 minutes to 1 to 2 hours, the obese may show "negative phases," *i. e.*, consume less oxygen. Such negative phases may occur during the day in obese people, while normal people do not show negative phases. The occurrence of the negative phases in obesity does not, however, explain the origin of obesity. It may be of value in estimating the 24-hour "basal" caloric requirement for the obese. If one estimates all the positive phases of metabolism on the one hand, and on the other hand all the negative phases during the 24 hours, the sum total of heat production may be smaller than indicated by the basal rate.

Water and Salt Retention. Gamble, Ross and Tisdall[20] have demonstrated certain facts regarding water metabolism. According to them the total of chemical bases is important in maintaining the structural integrity of body fluid. They computed the water weight lost during fasting in terms of fixed bases and thus were able to determine the amount of water lost from cellular content and intracellular storage. Figures in one of their cases show that 62 per cent of loss of body weight was due to loss of water. Loss of body water during the 15-day fast of epileptic child A. G., studied by Gamble, Ross and Tisdall:

	cc.
Intracellular water loss:	
Due to destruction of protoplasm	1620
Due to reduction of cell volume	470
	2090
Extracellular water loss	320
Total loss of body water	2410
Loss of body weight	3920 gm.
Body weight loss due to water	62 per cent

From metabolic studies in starvation it is known that not more than 400 to 500 gm. of solids may be lost in 24 hours, yet losses averaging twice that much are not uncommonly seen in the clinic.[21] It is clear that the great bulk of this must be water.

There are some obese patients in whom there is an unsuspected fluid and salt retention. Such patients when strictly dieted may actually be "undernourished," yet they suffer no loss of weight because of water storage. Van Noorden in 1910[22] has already warned about the importance of water and salt restriction in the treatment of obesity. Zondek[23] designated such patients as of the "salt water obesity type."

Bauer[24] speaks of them as cases of "hydrolipomatosis." An accurate account of the water exchange in the obese has recently been furnished by Newburgh and his associates.[25] They have shown that their obese patients, when losing body tissues on strict metabolic regimen, held or even gained weight due to water retention.

We have selected a small group of 7 patients who responded poorly to the usual dietary treatment of obesity. To demonstrate the possible water retention in these patients methods were employed that could be carried out in an outpatient clinic, private office, or in a general hospital that is not especially equipped for

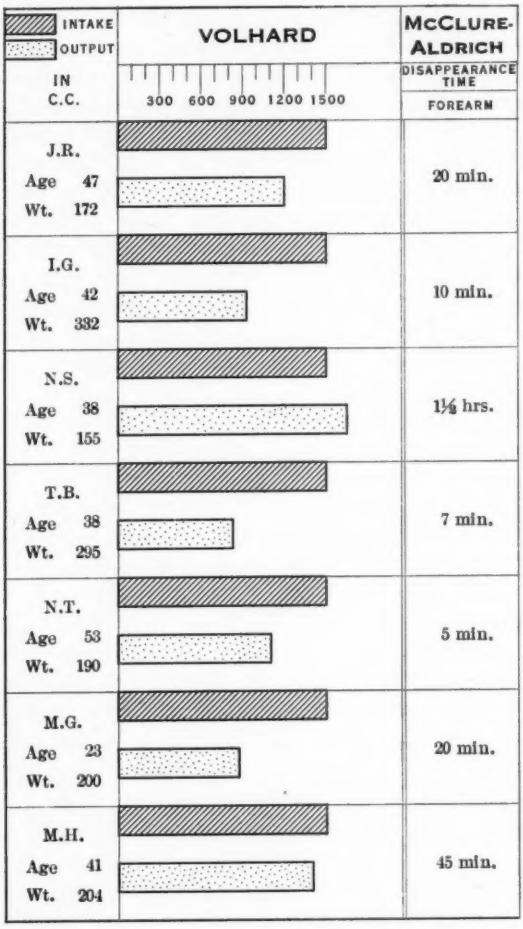

FIG. 1.—Volhard water test and McClure-Aldrich's intradermal salt solution test in 7 cases of obesity.

organized metabolic work. It is apparent that studies on water metabolism as recently described by Sunderman and Austin,[26] and Newburgh and his associates[27] could not possibly be undertaken on the material at hand.

The test for water retention was that of Volhard. In 5 out of the 7 patients there was a definite diminution in the urinary output

in the 4-hour period, the average patient showing a retention of 520 cc.

McClure and Aldrich[28] have shown that by injecting 0.2 cc. of 0.8 per cent salt solution intracutaneously into the flexor surface of the forearm and the inner surface of the calf muscle, a wheal appears which in normal persons remains an hour or longer. They

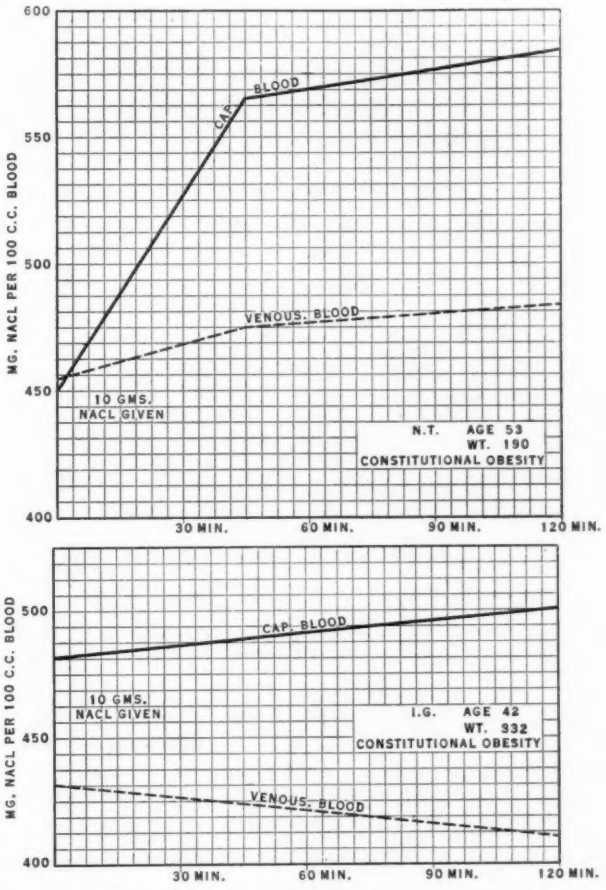

FIG. 2.—Sodium chlorid metabolism in 2 patients with obesity.

found that in renal edema the wheal disappears in a much shorter time. In our obese patients who tended to retain water the wheal disappeared in from 5 to 20 minutes after the salt solution injection.[29]

In 5 patients we studied the NaCl of the venous and of the capillary blood after the administration of 10 gm. of NaCl by mouth. Before the salt was given, the NaCl of the venous and capillary bloods were about the same.

After the ingestion of NaCl the patients behaved differently. Two of them showed a distinct difference, the venous blood containing 100 mg. and 90 mg. respectively less than the capillary blood, 2 hours after ingestion of NaCl.

In 1 patient the difference between the venous and capillary blood chlorid was not marked, and in 1 patient the capillary blood at the second hour was not determined, although the NaCl of the venous blood increased 40 mg. more than at the beginning of the test. Patient Mr. T. B. showed a constant concentration of venous NaCl (300 mg.). At the end of 2 hours the capillary NaCl rose to 375 mg., while the venous NaCl remained at the same level as before the administration of NaCl.

TABLE 3.—SODIUM CHLORID METABOLISM IN OBESITY.

Name.	Age, years.	Weight, pounds.	Capillary blood, mg. per 100 cc.	Venous blood, mg. per 100 cc.	Diagnosis.
T. B.	38	291	350	300	Cerebral obesity.
45 min. after ingestion of 10 gm. of NaCl	..	...	330	300	
120 min. after	..	...	375	300	
Mrs. T.	53	190	450	454	Constitutional obesity.
45 min. after ingestion of 10 gm. of NaCl	..	...	564	474	
120 min. after	..	...	564	474	
	..	...	584	484	
Mrs. M. G.	23	212	395	395	Cerebral obesity.
120 min. after ingestion of 10 gm. of NaCl	..	...	00 (not estimated)	430	
Mr. I. G.	42	332	480	430	Constitutional obesity.
120 min. after ingestion of 10 mg. of NaCl	..	...	500	410	
Mrs. M. H.	41	204	400	380	Thyroövarian obesity.
120 min. after ingestion of 10 gm. of NaCl	..	...	440	420	

It is noteworthy that the 2 patients who showed the retention of NaCl have lost considerable weight under the salt restriction and dehydration régime.

Di Foutsin[30] determined the NaCl after the administration of 15 to 35 mg. of NaCl in normal persons and found no difference between the capillary and venous blood during a period of $2\frac{1}{2}$ to 4 hours.

To increase the water elimination in obese persons who fail to reduce on diet alone, we use Salyrgan intravenously, as first suggested by Eppinger.[31] The diet is equivalent to approximately the basal caloric intake for a person of the desired weight. Thus, if the desired weight was 160 pounds, the patient's basal caloric intake would be approximately 1500 calories (20 calories per kilogram of body weight).

The amount of protein varies from 1 to $1\frac{1}{2}$ gm. per kilogram of desired body weight (in this instance 108 gm.). The difference in

calories between carbohydrate and fat is divided in ratio of 1 to 3, or carbohydrate 35 and fat 105, in this instance. The carbohydrate may be increased to 0.5 gm. to each gram of protein. The high protein keeps the patient in nitrogen equilibrium, and with the low carbohydrate favors water elimination.

The ketogenic-antiketogenic ratio of such a diet is less than 1.5 to 1 and is well tolerated. The fluid intake is limited to 1000 to 1200 cc. per 24 hours and the salt is restricted to 5 to 7 gms. daily.

Theocin may be used, but we found it objectionable, since it is apt to cause gastrointestinal disturbance.

We begin with 0.5 cc. of Salyrgan; if the urine fails to show evidence of kidney damage such as red blood cells and casts, the dose is increased to 1 cc. twice a week for 1 week, then 1 cc. every week for 2 weeks, and later one injection every month until the desired results are obtained.

The case below illustrates the apparent efficacy of Salyrgan in the treatment of certain types of obesity.

CASE 1.—Mr. T. M., aged 38 years; height, 5 ft. 7 in.; weight, 291 pounds. The patient complains of inability to keep awake and of constant gain in weight. In the past year he gained 100 pounds. With the increase in weight his drowsiness increased; he also developed polyuria, urinating nine to ten times during the day and five times on an average during the night. He claims to void about ½ pint of urine each time. He had influenza in 1917 and left otitis media in 1919. There was no history of obesity on either the maternal or paternal side of the family. He drinks large quantities of water during the day. According to his statement, his food is not excessive.

Physical Examination. The patient is a white male, aged 38 years, very obese, with marked tendency to girdle distribution. He has a short, thick neck. Body hair scanty; abdomen heavy and pendulous. The genitalia were normal.

Neurologic Examination (Dr. A. Silverstein). Pupils irregular, right reacts sluggishly to light. Labiofacial fold of right side less marked than left. Tremor of orbicularis muscle when patient shows his teeth. Upper extremities: Biceps and triceps reflexes markedly diminished, practically absent. Lower extremities: Knee jerks diminished on both sides. Some tenderness of fat deposits to palpation. All tests for sensation and cerebellar function were negative. The visual field examination was practically negative. The fundus examination (Dr. J. C. Rommel) shows that the media were clear; disks oval, the margins blurred and some swelling of the nerve head. Roentgen ray appearance of the sella turcica was normal. The basal metabolic rate was +30. Specific dynamic action of food 2 hours after mixed meal was 8(−) per cent. Sugar tolerance: Fasting specimen, 105.3; first hour after glucose, 148.1; second hour after glucose, 137.2; third hour after glucose, 80. Urinalysis: No abnormal findings. Blood chemistry: Sugar, 100; urea, 19; uric acid, 4.2; creatinin, 1.5. Sodium chlorid: Capillary blood was 350, venous blood 300. After 10 gm. of salt the capillary blood was 330 45 minutes later and 375 2 hours after. Venous blood, 300. Spinal fluid: Pressure, 8 mm. mercury; other findings negative. McClure-Aldrich test: Wheal disappeared in 7 minutes on forearm and 10 minutes on leg. Water retention: 500 cc.

The patient was placed on a diet of 1100 calories with restriction of fluids and salt. Diuretics, such as urea, have been used without apparent benefit. One cubic centimeter of Salyrgan was then given every 4 days for a period of 3 weeks. At the end of this period he had lost 29 pounds.

NOTE.—The patient had previously been in two hospitals with the hope of reducing his weight, but failed to lose any weight. He is still under observation and treatment in the Metabolic Clinic of the Temple University Hospital.

This case is apparently one of cerebral obesity. The symptoms of drowsiness and polyuria speak for a pathologic process in the region of the pituitary, infundibulum or paraventricular nuclei in the floor of the third ventricle. A mass lesion such as an intrasellar or suprasellar growth can be ruled out by the negative field studies and normal sella turcica by the Roentgen ray. In view of the fact that his symptoms of drowsiness and mental hebetude cleared considerably after the increase in fluid output would suggest that the hydrated condition of the brain was greatly lessened following treatment.

I used Salyrgan in 5 more patients with various types of obesity accompanied by water retention with good results.

An individual who retains water also has a tendency to deposit fat. Therefore, when he is dehydrated, he not only loses weight but is prevented from accumulating fat.

Water and salt metabolism, like temperature regulation, is governed by regulative centers in the central nervous system.

The polyuria and also glycosuria following a puncture in the floor of the fourth ventricle (Claude Bernard, 1835) are well known facts in point.

It was shown by Yungman and Erich Meyer[32] (quoted by Greving) that a puncture in the neighborhood of the nucleus of the visceral vagus not only produces polyuria but also an increase in salt elimination. The increase of the salt elimination is independent of the increase in urine elimination. Brugsh, Dresel and Lewy[33] believe to have shown that the centers for water and salt metabolism are present in the formatio reticularis.

There are centers in the hypothalamus for water and salt metabolism (Leshke). The exact location of these centers is not known. It is surmised that the centers are in the neighborhood of the supra-optic nucleus near the optic tract. Puncture of the caudate nucleus made by Reynolds and Spiegel[34] produced not only polyuria but also an increase of the salt elimination. This phenomenon was observed especially in those animals who showed also an elevation in temperature, proving that there is some relationship between the heat and salt and water metabolism centers.

The ability of the tissues to retain water is also believed to be regulated by certain centers in the central nervous system. The retention of water in the tissues is probably influenced by the

centers through the interaction of some of the glands of internal secretion.

We know that thyroxin diminishes water retention (Eppinger). The regulation of the water metabolism by the centers in the hypothalamus is therefore probably brought about through the action of endocrine glands. There is reason to believe that there are likewise centers in the hypothalamus for fat metabolism. The production of obesity in animals by injury to the hypothalamic region (tuber cinereum) without pituitary injury has been demonstrated by Smith.[35] The rôle that the pituitary gland plays in stimulating or inhibiting these centers is difficult to explain.

Raab[36] has shown that the injection of pituitrin is followed by an increased lipoid content of blood, probably due to an increased production of fat in the liver for ready use by the tissues. By depressing the heat center with antipyretics he found that the pituitary extract had no effect on the increased fat metabolism. One, therefore, may draw the conclusion that part of the heat center is concerned with fat metabolism.

The exact rôle the pituitary gland plays in the production of obesity is not definitely explained. It is known that Simmond's disease (marked cachexia) may arise as the result of lesions in the anterior lobe of the pituitary. It is also known that disease in the posterior lobe may produce marked obesity. These findings, like many pituitary phenomena are difficult to reconcile.

Conclusion. In obesity, though the law of conservation of energy is operative, *i. e.*, the balance between energy intake and energy output is disturbed, on the surface it is not apparent in some patients because they seem to gain in weight in spite of a low intake of food. Disturbances in water and salt metabolism with storage of water in the tissues should be borne in mind in such cases. In such patients the higher centers for fat metabolism, salt metabolism and water metabolism may be maladjusted (as in encephalitis). In the latter case it may often be related to the action of the product of some gland or glands of internal secretion. Obesity of hypothyroid nature seems to be infrequent. That some endogenous factor exists that would seem to account for some forms of obesity cannot be denied. Whether the endogenous factor is of constitutional nature and is associated with an endocrine disturbance, or the obesity is causing the latter is difficult to prove. Each case of obesity is a problem in itself, with regard to the basic causation and treatment. The general lines of management will include proper diet, proper exercise, restriction of fluid and salt, and in certain selected cases the administration of thyroid preparations. In certain cases the administration of Salyrgan in addition to diet and water and salt restriction seems to yield satisfactory results.

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THE CRAIG COMPLEMENT-FIXATION TEST FOR AMEBIASIS IN CHRONIC ULCERATIVE COLITIS.

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Chronic ulcerative colitis is an inflammatory disease of the lower intestine. It is characterized clinically by numerous rectal discharges of small liquid stools containing blood, mucus and purulent

exudate, also, by more or less fever, abdominal cramps, anemia, prostration and toxemia. It frequently terminates in the death of the patient from either toxic degeneration of vital organs, inanition, acute perforation, intestinal ileus or septicemia.

The chronic nature of ulcerative colitis, its resistance to treatment and the general failure to show a consistent etiologic factor have given rise to many speculations as to the initial cause of the disease. Some have considered the disease to be a chronic stage of bacillary dysentery. Shiga has reported that the bacillary disease may sometimes become chronic although the initial causative organism, which is very easily overgrown, may not be found after the first few days following the onset of the acute stage. Although the Bacillus dysenteriæ does not persist long in the stools it would seem that the chronic cases would be more apt to show a specific agglutination reaction in the serum. Hawkins, however, did not find this to be true in the sporadic cases of ulcerative colitis occurring in England at least.[1] Silverman[2] has reported that apparently several strains of the bacilli of dysentery are accountable for sporadic cases occurring in the southern States. He was able to recover from such cases the bacilli of Shiga, Flexner, Morgan and Duval or Sonne, and agglutinating reaction supported the diagnoses. However, the clinical relationship between such cases and cases of the disease known as chronic ulcerative colitis is problematical. Hurst,[3] having noticed a marked similarity in the proctoscopic appearances of the rectal mucosa in chronic bacillary dysentery and idiopathic chronic ulcerative colitis, reports that he treats all of his cases of the latter disease with specific antibacillus dysentery serum with "miraculous" results in some cases. He uses the serum in large intravenous doses producing, in many cases, marked foreign protein reactions. Since those who work with the acute bacillary disease have found that serum therapy is practically valueless after the first few days following the onset, it may be possible that the good results which Hurst obtains in the chronic condition are due to the nonspecific reaction to a foreign protein. The similarity of the proctoscopic appearances in the two conditions can be explained on the basis that both diseases are purulent inflammations of the mucous membrane with extension to the underlying tissues and in the chronic stage the process is so modified by secondary infection that the pathology in the colon becomes much the same.

Within the last few years the interest in the bacteriology of colon disease has been greatly stimulated by the work of Bargen[4,5] of the Mayo Clinic. He has reported that in a large proportion of cases he has been able to isolate from the ulcerations in the colon a diplostreptococcus with fairly definite morphologic and cultural characteristics. Paulson[6] has been able to isolate many different strains of enterococcus which will produce colitis in animals. Some of these strains were obtained from normal healthy individuals and

from infections outside the gastrointestinal tract. The bacteriology of the colon is a complicated difficult problem and much work has yet to be done before the bacterial etiology of ulcerative colitis is either definitely established or definitely disproved.

That chronic ulcerative colitis is a chronic form of amebic dysentery is another conjecture that has some features suggesting that it is within the realms of possibility. Amebic dysentery is now known to be more widely spread than was formerly realized and it has been fairly definitely proven that from 5 to 10 per cent of the population of the United States harbor the Amœba histolytica. Although in the early stages of amebic dysentery and ulcerative colitis the appearance of the mucosa as viewed through the sigmoidoscope may be sufficiently different to be diagnostic, in the later stages when superimposed secondary infection has greatly modified the amebic disease, it is almost impossible to make a differential diagnosis by means of the sigmoidoscopic examination.

In the acute case of amebic dysentery a competent protzoölogist usually has no difficulty in demonstrating the etiologic agent, and in many of the chronic cases pathogenic amebæ are present in greater or lesser numbers. However, in some of the chronic cases the finding of either the vegetative forms or cysts becomes exceedingly difficult. Even material obtained by scraping the ulcers, a procedure which is often fruitful when the stools are negative, fails to show the amebæ in some definitely proven cases of amebiasis. In 2 of Councilman and Lafleur's[7] cases amebæ were not found in the stools or in sections made of the intestinal ulcers, but were found to be present in liver abscesses. If the liver abscess had not been present a diagnosis of amebiasis would not have been justified even though the intestine was ulcerated. Hutchison[8] also reports a case of amebic dysentery which came to autopsy which showed extensive ulceration of the colon, but no amebæ were found in any of many sections. Both Hutchison[8] and Callender,[9] in their papers on amebic dysentery, suggest as an explanation for this paucity of amebæ the prominent part that secondary infection plays in the chronic stage. They have found that the amebæ enter the tissues by lysis and with little leukocytic reaction. They spread through the lymph channels of the submucosa. The symptoms of dysentery arise when the initial lesion is invaded by secondary pyogenic organisms. The amount of destruction and reaction depends upon the character of the secondary invader, which causes the spread of the ulcer so that the tissue damage becomes out of all proportion to the number of amebæ present. Amebæ are always scarce in the presence of active suppuration and absent where there is granulation tissue. For this reason the failure to find amebæ in the stools is not sufficient evidence upon which to make a differential diagnosis.

The late changes in the colon are also much the same in the two diseases. The intestinal wall becomes much thickened with the formation of a straight, narrow, inflexible lumen. Polypi have been

reported to arise in the long-standing cases of both conditions with occasional carcinomatous degeneration.[7,10]

Since a review of the literature indicated that there was nothing in either the clinical course of the disease, the microscopic examination of the stools, the bacteriologic examination of the infected material or the sigmoidoscopic examination of the intestinal mucosa that conclusively differentiated between chronic amebic colitis and chronic ulcerative colitis, the author has employed a complement-fixation reaction recently advanced by Craig as diagnostic of amebiasis. This test has been applied to the sera of 19 patients who clinically and sigmoidoscopically were characteristic cases of chronic ulcerative colitis and the real purpose of this paper is to report the results of this test in correlation with the results of other clinical and laboratory findings and with the results of anti-amebic therapy.

In a report on the results of his test, Craig[11] gives the results of the test on 689 patients. In 84 (12 per cent of this group) the complement-fixation test was 3+ or 4+ positive. Any reaction less than 3+ positive he considers undiagnostic. Of the 84 cases with positive complement-fixation test, 92 per cent showed Endamœba histolytica in the stools. In the remaining 8 per cent the stools were possibly insufficiently examined. In the 605 cases with negative serologic findings the Endamœba histolytica was present in only 0.8 per cent. The test, when applied to patients with acute or chronic diseases of other types and with other types of protozoal infections, gave uniformly negative results except in some patients with a positive Wassermann reaction.

In all instances reported in this paper the serologic tests were done by Dr. Craig's laboratory in the Army Medical School, on sera sent by mail from Boston to Washington. The stool examinations were made either personally or by the pathologic laboratory of the New England Deaconess Hospital under the direction of Dr. Shields Warren. In most instances the stools were examined both microscopically and culturally for amebæ by Dr. Lemuel R. Cleveland of the Harvard School of Tropical Medicine.

In our series of 22 cases which were diagnosed chronic ulcerative colitis by clinical, proctoscopic or postmortem examination, Endamœba histolytica were found in the stools of 3. This does not include cases of definite amebic dysentery with characteristic amebic ulcers in the rectum and sigmoid.

These 3 cases all showed a positive Craig test. In the series there were, all told, 19 cases on whom the Craig test was done. There were 15 positives, that is, 4+ or 3+ reactions, which Craig considers diagnostic, and 4 with either negative, + or 2+ reaction, which are not diagnostic.

The 4 cases who gave a negative or only 1+ or 2+ reactions were not clinically different from the larger number of cases giving a definitely positive reaction.

Case No.	Age.	Sex.	Symptoms.	Severity by proctoscopy.	Extent by Roentgen ray.	Complement-fixation.	Treatment.	Duration of follow-up; results.
1 . . . (6681)	21	F	Bloody diarrhea for 10 weeks; fever; prostration; amebæ in stools	Not done	Entire colon	++++	Antiamebic drugs; transfusion; ileostomy	Death from toxemia; autopsy showed typical ulcerations of colitis but amebæ in tissues.
2 . . . (14817)	38	F	Recurrent bloody diarrhea since childhood; anemia; amebæ in stools	++ Polyposis	Entire colon	++++	Treatment refused	
3 . . . (14044)	54	M	Recurrent bloody diarrhea for 25 years; marked anemia; no amebæ in stools	++	Entire colon	++++	Diet; iron; antiamebic drugs	16 months; excellent remission; no recurrence.
4 . . . (14693)	37	F	Recurrent bloody diarrhea for 5 years; anemia; no amebæ in stools	++	Entire colon	++++	Diet; antiamebic drugs	16 months; fair remission with 3 recurrences and stenosis of rectum.
5 . . . (12832)	26	F	Stenosis of rectum; anemia; history of bloody diarrhea; no amebæ in stools	Not done	Sigmoid and rectum	+++	Ileostomy; diet; iron	18 months; rectal abscess with recovery; condition very good.
6 . . . (16020)	38	F	Bloody diarrhea for 3 months; prolapse of rectum; anemia; no amebæ in stools	++	Entire colon	++++	Diet; iron; antiamebic drugs	Not heard from since; good remission.
7 . . . (14585)	8	M	Bloody diarrhea for 10 months; anemia; no amebæ in stools	++	Entire colon	++++	Diet; antiamebic drugs	16 months; excellent remission; no recurrence.
8 . . . (14600)	46	F	Bloody diarrhea for 6 months; loss of weight; no amebæ in stools	Normal	Ascending and transverse	++++	Diet; antiamebic drugs	12 months; improved; some recurrences of diarrhea; gain in weight.
9 . . . (16506)	31	M	Bloody diarrhea for 4 years; no amebæ in stools	+++ Carcinomatous degeneration	Rectum	++++	Resection of rectum	12 months; complete relief; (epidermoid carcinoma).

10 . . . (16930)	46	M	Recurrent bloody diarrhea for 20 years; anemia; fever; no amebæ in stools	+++	Entire colon	++++	Diet; antiamebic drugs; transfusion	12 months; good remission; no recurrences.
11 . . . (16562)	25	F	Bloody diarrhea for 7 months; anemia; no amebæ in stools	++	Entire colon	++++	Diet; antiamebic drugs	9 months; excellent remission; no recurrence.
12 . . . (17706)	20	F	Bloody diarrhea for 4½ months; vomiting; fever; anemia; no amebæ in stools	+++	Entire colon	++++	Diet; sedatives; antiamebic drugs; transfusion	11 months; improved, but still has some diarrhea and bleeding.
13 . . . (17705)	37	F	Diarrhea for 1 year; fever; prostration; anemia; amebæ present	++	Entire colon	++++	Diet; antiamebic drugs	10 months; improved with occasional diarrhea.
14 . . . (21122)	30	F	Bloody diarrhea for 9 weeks; vomiting; fever; moribund	Not done	Not done	++++	None	Death from perforation; autopsy; marked ulceration and necrosis of colon; no amebæ found.
15 . . . (21039)	48	F	Bloody diarrhea for 2 months; fever; prostration; anemia; no amebæ in stools	Normal	Ascending colon	++++	Diet; antiamebic drugs; transfusion	1 month; good remission.
16 . . . (7529)	48	M	Recurrent bloody diarrhea for 26 years; fever; prostration; no amebæ in stools	++++	Entire colon	+	Diet; vaccine; ileostomy.	Death from toxemia; no autopsy.
17 . . . (8268)	42	F	Bloody diarrhea for 5 months; anemia; no amebæ in stools	++	Entire colon	++	Ileostomy; antiamebic drugs	28 months; improved; several recurrences.
18 . . . (19854)	25	F	Diarrhea for 3 months; fever; prostration; no amebæ in stools	Normal	Ascending and transverse	+	Ileostomy	6 months; bloody rectal discharge; condition excellent.
19 . . . (20306)	62	F	Recurrent bloody diarrhea for 1 year; no amebæ in stools	+	Entire colon	+	Diet; other treatment not tolerated	1 month; some improvement.

Besides the 19 cases of ulcerative colitis we have seen 3 other patients who gave a 4+ complement-fixation test. All 3 of these patients suffered from abdominal distress and intermittent attacks of diarrhea, but the stools were negative for blood or for the amebæ. One of them gave a history of a definite attack of acute amebic dysentery occurring in the tropics a few months previously and it is doubtful if she was entirely cured. The second patient had had attacks of diarrhea for years without gross blood being noticed at any time. The third patient died of chronic diarrhea and inanition and the autopsy showed no evidence of amebic infection or of ulcerative colitis.

We have also sent to Dr. Craig several sera from patients with diarrhea caused by functional disorders of the colon and he has reported them consistently negative.

We have also had one patient with diarrhea and Amœba histolytica in the stools who gave only a 2+ reaction.

The results of treatment of chronic ulcerative colitis are far from satisfactory, and no form of therapy yet tried has given uniformly good results, although almost any form of treatment will apparently bring about improvement in a certain proportion of cases.

The author is of the opinion that many clinicians throughout the country have used antiamebic drugs in cases of chronic ulcerative colitis even though they have been unable to demonstrate the ameba in the rectal discharges. It would be interesting to know in what percentage of cases such drugs have proved to be beneficial. We have treated most of our cases with emetin intramuscularly, acetarsone or stovarsol and bismuth by mouth, and in a few cases yatren has been used as a rectal infusion. In conjunction with these drugs we have used a low residue, high vitamin, bland diet and have used belladonna and opium in small quantities. Great caution should be exercised in basing any conclusions on the apparent benefit of any given form of treatment in a disease such as this. It may suffice to say that antiamebic drugs were used in 11 cases in this series. Four of these have had a complete remission of symptoms for from 10 to 14 months. Five others have been definitely improved but still have some diarrhea with occasional bleeding. One other has not been much improved but has not taken much treatment and has only been followed for 1 month. The other is at present under treatment in the hospital and is apparently recovering satisfactorily.

Although there is no proved relationship between ulcerative colitis and intestinal amebiasis, we believe antiamebic treatment should be tried in all cases suitable for medical treatment. The significance of the Craig test when amebæ cannot be found in the stools is still very much unsettled, but the results of the test when applied to cases of chronic ulcerative colitis are reported here with the hope that they will shed some light either upon the disease in

question or upon the specificity of the test itself. Craig admits that the serologic test which he has devised is difficult, and unless closely controlled is apt to give erratic results. It undoubtedly will require further verification before its actual value can be determined, particularly since his antigens are not made from bacteria-free cultures of amebæ. It may be that the positive reactions obtained in ulcerative colitis have more to do with a bacterial antigen than with the amebic antigen. On the other hand, the concept that ulcerative colitis is a superimposed secondary infection of a primary amebic ulceration of the colon seems to be within the realms of possibility, particularly since British soldiers serving in Egypt and Gallipoli have been known to suffer an acute attack of amebic dysentery with apparent recovery, and later to develop a chronic ulcerative colitis from which only streptococci could be obtained.[12] Whether or not the secondary bacterial invader is always the same is another phase of the complicated question. It may be that a specific organism, normally resident in the human intestine, sets up an inflammatory process in the intestinal wall only when certain opportunities such as an amebic ulceration occur.

Summary. That it is extremely difficult to differentiate between chronic ulcerative colitis and chronic amebic colitis has been pointed out and discussed.

The result of the Craig complement-fixation test for infection with Endamœba histolytica when applied to patients with chronic ulcerative colitis is reported showing that 15 out of 19 cases gave a strongly positive reaction.

No conclusions as to the significance of this finding are drawn, but it is suggested that chronic ulcerative colitis may be a pyogenic infection of the colon superimposed upon an original amebic ulceration.

Abstracts of the case histories of the 19 cases tested are reported.

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A STUDY OF THE CAPILLARY PRESSURE IN NEPHRITIS AND HYPERTENSION.

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This investigation represents a further attempt to correlate variations of the blood pressure within the minute vessels with the clinical findings in acute and chronic nephritis and in essential hypertension. Special attention has been given to the influence of capillary pressure on the development of edema.

Many methods are available for the study of the blood pressure of the capillary. As in previous work,[1,2] the closed capsule method[3] has been used in making individual readings while visualizing the capillary at the base of the nail by means of a binocular microscope. The hand is kept at the level of the heart and constant temperature conditions are maintained. The pressure is read when the flow of blood is reëstablished upon releasing the obstructing pressure in the closed capsule. Many observations were made, but only the most frequently recurring reading has been charted. Although the accuracy of the method has been questioned, Landis[4] has shown by means of intracapillary pipettes that the blood pressure at the bend of the capillary loop corresponds with those made by the indirect method.

The same apparatus has been used in determining the venule pressure in the subpapillary plexus. It is agreed that the color of the healthy skin is dependent largely upon the blood in the subpapillary venous plexus. To read the pressure of the venules, the capsule is first inflated until the skin is rendered colorless. Reducing the pressure slowly, at the first appearance of color in the skin the pressure is read on the manometer and considered the venule pressure. These readings on normals have been found to correspond to those of Landis obtained in the venous limb of the capillary. This method differs from that of Lewis and Hynal[5] in the criterion used in reading the pressure. These authors made their reading at the first diminution in skin color, determining in this way the amount of pressure necessary to overcome the resistance of the venule wall. The method employed in our studies gives the pressure necessary to reestablish the bloodflow, the procedure used in determining the pressure in the brachial artery. Several opportunities arose where it was possible to make pressure readings by observation of the bloodflow in the venule. These readings have differed only by 1 or 2 mm. of mercury from those found by the blanching method.

TABLE 1.—HYPERTENSION CASES.

Hospital No.	Case No.	Age, yrs.	Vascular system.			Urine.			Hemoglobin, per cent.	R.b.c., millions.	Kidney function.		Serum protein, per cent.	Capillary pressure, mm. Hg.	Capillary morphology.	Venule pressure, mm. Hg.	Edema.	Notes.
			Eye grounds.	Radial.	B.P.	Alb.	R.b.c.	Casts.			2-hr. phthal.	Urea, mg. per 100 cc.						
130600	3	35	Neg.	Neg.	145/90	s.p.t.	Occ.	0	85	4.5	65	23	8.1	15	Slight tortuosity	..	0	PH tox. of pregnancy.
232419	6	41	A_{++++}*	Neg.	255/140	0	0	0	100	6.0	60	22	8.1	10–15	Small, beaded, narrow arterial limb	..	0	
238765	7	19	...	...	160/90	..	..	..	89	5.1	..	18	7.9	30	Narrow arterial limb, rapid flow			
207798	35	..	Slight A*	A_{+}*	168/120	0	0	0	..	5.7	55	22	7.2	25	Tortuous and normal types	..	0	
181448	48	33	A_{++}*	Neg.	200/120	t.	+	0	..	5.5	65	38	6.7	28	Normal	15	0	
260175	48A	..	A_{+}*	+	250/140	f.t.	0	0	93	5.4	..	24	..	25	Normal	15	0	
185742	23	30	...	Neg.	210/120	v.f.t.	Occ.	..	85	5.2	75	28	7.4	25 and	Large narrow arterial wide venous loops	..	0	
71187	26	43	A_{++}* Exudate	A_{+}*	210/160	v.f.t.	0	Occ.	..	4.2	55	45	7.4	25	Narrow, rapid flow	12	0	
71296	29	35	A_{+++}*	Neg.	240/130	v.f.t.	0	Occ.	..	4.7	65	..	..	25	Dilated and tortuous	5	0	Hand red.
88738	30	12	Neg.	Neg.	148/80	0	0	0	..	5.1	65	26	7.1	25	Dilated venous limb	12	0	Bier's spots on arm.
48653	41	45	A_{++}* Exudate	A_{++}*	230/140	v.f.t.	0	0	..	5.8	46	32	7.0	30	Narrow arterial limb	12	0	
255353	42	..	Neg.	Neg.	200/110	f.t.	0	0	90	5.5	60	33	..	20	Narrow arterial limb	15	0	
61277	43	36	A_{+++}*	A_{+++}*	180/125	f.t.	+	0	..	5.5	60	26	..	35	Normal	18	0	

* A = arteriosclerosis.

TABLE 2.—ACUTE NEPHRITIS CASES.

Hospital No.	Case No.	Age, yrs.	Vascular system.		Urine.			Hemoglobin, per cent.	R.b.c., millions.	Kidney function.		Serum protein, per cent.	Capillary pressure, mm. Hg.	Capillary morphology.	Venule pressure, mm. Hg.	Edema.
			Radial.	B.P.	Alb.	R.b.c.	Casts.			2-hr. phthal.	Urea, mg. per 100 cc.					
237603	8	19	Neg.	110/70	t.	0	0	75	2.8	40	...	6.5	15	Normal, rapid	...	0
33338	13	...	+	130/95	t.	+	+	90	6.6	50	30	8.1	30–35	Small, tortuous	...	0
32305	37	26	Neg.	130/90	t.	+++	0	...	5.8	55	28	7.4	20–25	Normal	10	0
25211	47	..	Tense	115/70	t.	+++	0	...	...	...	..	4.1	30	Venous limb dilated	15	+
237603	25	19	Neg.	110/80	t.	+	+	...	4.0	...	39	6.6	35	Long, narrow arterial limb	10	0
252134	39	...	Neg.	160/130	v.h.t.	++++	+	105	5.7	15	54	4.2	30	Narrow arterial limb, flow rapid	15	+
	39A	...	Neg.	135/95	v.h.t.	++++	+	51	3.0	...	90	...	20	Beaded flow	8	+
289338	N9	...	Neg.	146/90	h.t.	+++	+	83	4.1	70	37	5.9	35	Normal	20	0

TABLE 3.—CHRONIC NEPHRITIS CASES.

Hospital No.	Case No.	Age, yrs.	Vascular system.			Urine.			Hemoglobin, per cent.	R.b.c., millions.	Kidney function.		Serum protein, per cent.	Capillary pressure, mm. Hg.	Capillary morphology.	Venule pressure, mm. Hg.	Edema.	Notes.
			Eye grounds.	Radial.	B.P.	Alb.	R.b.c.	Casts.			2-hr. phthal.	Urea, mg. per 100 cc.						
12857	5	29	A*	A_{++}*	150/100	f.t.	0	0	83	4.8	53	46	6.3	25	Normal	..	0	
198959	11	39	A*	A_{+}*	210/120	t.	+	+	85	4.6	45	58	5.8	35	Many dilated	..	0	
144483	12	27	Neg.	Neg.	126/100	t.	+	+	110	6.4	60	28	7.2	30–35	Large tortuous arterial limb narrow, flow slow	..	0	
84270	14	18	Neg.	Neg.	110/60	t.	0	0	80	5.0	70	22	7.8	20	Arterial limb narrow	..	0	
244825	15	30	Neg.	Neg.	230/150	t.	+	+	..	5.5	45	31	7.2	30	Few with narrow arterial limb	..	0	
247165	18	28	A_{+}*	A_{++}*	220/160	t.	0	+	..	4.4	18	40	6.4	40	Narrow equal limbs	..	0	PH eclampsia.
	18A	..	...	..	230/130	h.t.	0	1	..	..	..	103	6.3	50	Thread-like	20	+	2 wks. ago had spontaneous abortion of 2 mos. pregnancy; terminal uremia.
242072	20	32	Neg.	Neg.	120/95	0	++	0	..	5.0	55	32	6.8	20–15	Normal	..	0	Chr. sinus infection.
	21	..	Neg.	Neg.	130/80	t.	++	+	85	5.6	60	31	6.8	25	Normal	..	0	
69319	22	21	A_{+}*	Neg.	220/130	t.	0	++	62	3.1	7	96	5.8	35	Tortuous	..	+	
71995	32	27	Neg.	A_{++}*	112/70	t.	+	++	..	5.9	..	...	..	25	Tortuous	..	0	
247097	33	..	A_{+++}*	A_{+}*	140/100	t.	0	+	50	2.8	..	250	5.6	45	Slight tortuosity, flow rapid	20	+	Recurrent hydrothorax; p.h. hypertensive toxemia of pregnancy.
264818	49	..	Neg.	Neg.	115/85	t.	+	+	60	4.0	65	38	4.3	20	Narrow, slight tortuosity	..	0	

264818	49	..	Neg.	Neg.	115/85	t.	+	+	60	4.0	65	38	4.3	20	Narrow, slight tortuosity	..	0	ax; p.n. hypertensive toxemia of pregnancy.
215431	50	..	....	..	210/140	t.	+	+	88	5.4	50	48	..	20	Large, dilated capillaries	20	0	Vasomotor spasm of hands.
57385	51	..	Neg.	Neg.	130/75	t.	0	0	96	5.1	55	39	6.7	22	.....	15	0	
54474	52	..	Neg.	A_+*	125/80	t.	0	+	95	5.6	55	45	6.8	25	Large, dilated capillary	20	0	
244825	54	..	A_+*	A_+*	230/150	h.t.	+	+	..	..	45	31	7.2	35	.....	20	0	
194266	24	..	Neg.	Neg.	100/60	t.	0	0	104	5.9	65	29	7.1	25	Arterial limb slight narrowing	10	0	
63581	27	33	A_+*	Neg.	130/70	t.	+	+	..	4.0	15	59	..	15	Flow is slow	10	0	Hand cool.
256633	38	..	A_{+++}*	A_{++}*	190/84	h.t.	+	+	75	3.5	..	50	4.4	40	Slight tortuosity	15	0	
242134	28	22	A_{+++}*	A_{++}*	200/150	t.	++	+	90	4.6	45	39	7.1	35	Narrow, not numerous	12	0	1 week ago acute pharyngitis.
	28A	..	....	..	180/130	h.t.	+	+	80	4.3	..	61	5.0	20–25	Venous limb dilated	8	+	Terminal uremia.
84878	1A	..	Neg.	Neg.	130/90	t.	0	+	61	3.2	60	30	4.0	25	Arterial limb narrow, flow slow	..	+	Transfusion last week.
	1B	..	....	..	120/90	t.	0	0	83	4.5	..	..	6.0	25	.....	..	0	
	1C	..	....	..	140/110	t.	0	+	70	3.8	..	..	6.0	30	.....	..	+	
75568	10	..	Neg.	Neg.	180/110	f.t.	+	+	50	2.2	..	68	6.1	40	Few capillaries; venous limb dilated	..	0	Nervous and pale.
241392	45	..	Neg.	Neg.	180/110	t.	+++	+	95	4.3	22	40	6.3	35	Arterial tortuous venous limb dilated	20	0	
277228	N1	..	Neg.	Neg.	140/100	h.t.	0	0	70	3.6	..	14	5.6	50	Both limbs narrow, rapid flow	25	2	
75211	N2	..	....	..	110/70	h.t.	+	+	..	..	..	..	4.7	28	Narrow-beaded flow	15	2	Sinus infection.
	N3	..	Neg.	Neg.	120/80	h.t.	Occ.	Occ.	70	3.2	..	53	4.7	35	Narrow rapid flow	20	1	Sinus infect. clearing.
75568	N4	..	....	..	148/105	h.t.	+	+	45	2.5	..	..	6.4	35	.....	25	1	
279754	N5	..	A_+*	++	190/130	h.t.	+	Occ.	96	4.5	..	35	4.0	35	Normal-beaded	20	3	
	N6	..	....	..	135/90	h.t.	+	Occ.	84	4.2	..	41	5.5	20	Rapid, beaded	10	0	Acute sinusitis; T. 100.
242073	N7	..	....	..	110/90	t.	+	+	86	5.4	..	51	4.8	30	Normal, slow	15	1	Rhinitis.
289319	N8	36	A_{++}*	++	290/180	h.t.	+	0	73	3.8	20	4	6.0	45	Narrow, rapid	25	2	

* A = arteriosclerosis.

TABLE 4.—CARDIAC DECOMPENSATION CASES.

Hospital No.	Case No.	Age, yrs.	Vascular system.			Urine.			Hemoglobin, per cent.	R.b.c., millions	Kidney function.		Serum protein, per cent.	Capillary pressure, mm. Hg.	Capillary morphology.	Venule pressure, mm. Hg.	Edema.
			Eye grounds.	Radial.	B.P.	Alb.	R.b.c.	Casts.			2-hr. phthal.	Urea, mg. per 100 cc.					
1336	55	64	A_{++}*	++	210/100	h.t.	0	+	95	3.9	..	59	5.5	40	Venous limb dilated	40	++++
	55A	...	...	..	180/100	t.	0	..	...	...	..	65	5.6	45	.....	40	+++
69047	58	34	Neg.	Neg.	180/100	h.t.	+	+	88	4.0	40	36	...	28	.....	28	+

* A = arteriosclerosis.

The osmotic pressure of the blood is determined by the amount of its crystalloid and colloid constituents. The crystalloids can be ignored as they are counterbalanced in the tissue spaces in accordance with the Donnan equilibrium. The effective osmotic pressure of the serum is dependent upon the concentration of its protein fractions—albumin, globulin and fibrinogen. In our studies the total serum protein concentration was measured.

The cases studied have been grouped according to clinical diagnosis, and together with physical and laboratory findings, tabulated in Tables 1, 2, 3 and 4.

Results. In the group of patients with essential hypertension no typical capillary morphology was found, *i. e.*, neither the shapes of the capillaries nor the type of bloodflow was distinctive. The arterial limb was usually narrower than the venous limb. The presence of scleroses in the radials or retinal vessels was not constantly associated with any tortuosity or other characteristic change in the form of the capillary. The height of the brachial and capillary pressures showed no constant relationship. The capillary pressure in this series of cases was found in most instances to be near the upper limit of normal, although in a few it was abnormally increased. Neither the cases with high or normal capillary pressure presented any associated significant physical or laboratory findings. The serum proteins were normal in concentration and no edema was present.

The cases of acute nephritis were either in an active or a convalescent stage. The radials and retinal arteries showed no abnormality. No constant morphologic change was present in the capillaries in either stage. The eye grounds were negative in every case. In Case 39 there was severe renal bleeding of 3 days' duration. Table 5 shows that the active cases had blood and albumin in the urine and that their capillary pressures were increased in all instances. Edema was present where the increased capillary pressure was associated with a low serum protein. The venule pressures were normal.

In the cases of chronic nephritis the capillaries though often tortuous presented no consistent morphology, nor did they show any constant relationship to the state of the peripheral vessels. The cases as analyzed in Table 6 fall into two groups, either a normal or a high capillary pressure. Hematuria was present in about one-half of the first group and in about two-thirds of the patients of the second group. By far the greater number of cases with poor kidney function had a high capillary pressure. Thirteen cases had edema. Ten of these patients had a high capillary pressure which was associated in 3 instances with a low serum protein, in 6 with slightly decreased serum protein and in 1 with a normal protein concentration. To show more clearly how the variations in degree of edema were associated with coincident variations in capillary

TABLE 5.—ACUTE NEPHRITIS.

	Blood pressure, mm. Hg.	Capillary pressure, mm. Hg.	Serum protein, per cent.	Edema.	Venule pressure, mm. Hg.
		Active Cases.			
39 . . .	160/130	30	4.2	+	15
47 . . .	115/70	30	4.1	+	15
25 . . .	110/80	35	6.6	0	10
13 . . .	130/95	30	8.1	0	
N9 . . .	140/90	35	5.9	0	20
		Convalescent Cases.			
37 . . .	100/90	20	7.4	0	10
8 . . .	100/70	15	6.5	0	

TABLE 6.—CASES OF CHRONIC NEPHRITIS.

No.	Blood pressure.	Capillary pressure.	Serum protein, per cent	Edema.	Urine.		Kidney function.
					Alb.	R.b.c.	
27 . . .	130/70	15	..	0	t.	1	Markedly impaired.
14 . . .	110/60	20	7.8	0	t.	0	Normal.
20 . . .	120/95	20	6.8	0	0	1	Normal.
49 . . .	115/85	20	4.3	0	t.	1	Normal.
50 . . .	210/140	20	..	0	t.	1	Normal.
N6 . . .	135/90	20	5.6	0	h.t.	1	Normal.
51 . . .	130/75	22	6.7	0	t.	0	Normal.
5 . . .	150/100	25	6.3	0	f.t.	0	Normal.
21 . . .	130/80	25	6.8	0	t.	1	Normal.
32 . . .	112/70	25	..	0	t.	1	
52 . . .	125/80	25	6.8	0	t.	0	Normal.
24 . . .	100/60	25	7.1	0	t.	0	Normal.
28a . .	180/130	25	5.0	1	h.t.	1	Markedly impaired.
1a . .	130/90	25	4.0	1	t.	0	Impaired.
1b . .	120/90	25	6.0	0	t.	0	Impaired.
N2 . . .	110/70	28	4.7	2	h.t.	2	Impaired.
15 . . .	230/150	30	7.2	0	t.	1	Normal.
1c . .	140/110	30	6.0	1	t.	0	Impaired.
N7 . . .	110/90	30	4.8	1	t.	2	Impaired.
11 . . .	210/120	35	5.8	0	t.	1	Impaired.
12 . . .	126/100	35	7.2	0	t.	1	Normal.
22 . . .	220/130	35	5.8	1	t.	0	Markedly impaired.
54 . . .	230/150	35	7.2	0	h.t.	1	Normal.
28 . . .	200/150	35	7.1	0	t.	2	Markedly impaired.
45 . . .	180/110	35	6.3	0	t.	3	Impaired.
N3 . . .	120/80	35	4.7	1	h.t.	1	Impaired.
N4 . . .	148/105	35	6.4	1	h.t.	2	
N5 . . .	190/130	35	4.0	3	h.t.	1	Normal.
18 . . .	220/160	40	6.4	0	t.	0	Markedly impaired.
38 . . .	190/84	40	4.4	0	h.t.	1	Markedly impaired.
10 . . .	180/110	40	6.1	0	f.t.	1	Markedly impaired.
33 . . .	140/100	45	5.6	1	t.	0	Markedly impaired.
N8 . . .	290/130	45	6.0	2	h.t.	2	Normal.
18*a* . .	230/130	50	6.3	1	h.t.	0	Markedly impaired.
N1 . . .	140/100	50	5.6	2	h.t.	0	Markedly impaired.

pressure and serum protein, the clinical course of Case 33 is graphically presented in Chart I. The theoretical significance of this will be discussed later. An opportunity arose during this investigation to note in several cases a difference in response of the capillary pressure to stress during the course of their disease. Case 28, after a 2 months' pregnancy, had a rise in capillary pressure, the hypertensive reaction usually found in toxemias of pregnancy. Cases 18, N1 and N2, following an acute pharyngitis, had a drop in capillary pressure. The clinical picture, however, in both types was similar.

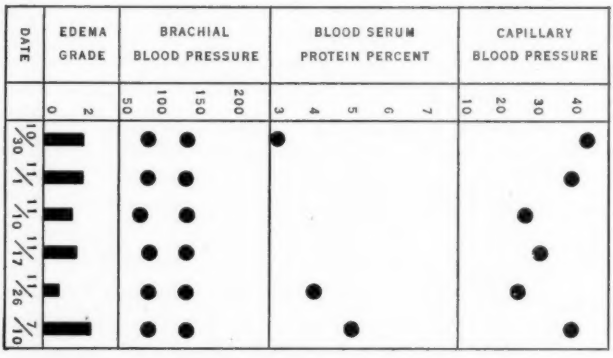

CHART I.—Case 33. Graphic relationship of edema and other factors.

In the cases of nephritis with cardiac failure studied the venule pressure was increased to the level of the capillary pressure, which in 1 case was normal and in the other was abnormally high. The increase in venule pressure in cardiac decompensation has been observed by other investigators.

Discussion. The literature concerning capillary morphology in hypertensive disease is extensive. A beaded type of bloodflow and varieties of shapes of loops during the active illness have been described[6] with a return to normal upon the subsidence of the clinical condition. Our observations have not confirmed these findings. However, the capillary morphology has helped explain the pallor that is present in the patients with a nephrotic type of renal disease. The pallor is much more marked than one would expect from the hemoglobin and red blood cell count. The capillaries were found to be few in number and so threadlike in diameter that it has been impossible to make pressure readings on them. A case of pernicious anemia with a similar grade of pallor showed many more capillaries at the nail base. The pallor appears to be due to a paucity and extreme contraction of skin capillaries resulting in a decreased flow of blood in the skin. Whether these capillaries are in a spastic state or are permanently narrowed is difficult to say.

From a consideration of the morphology and blood pressure of the capillaries in the cases of essential hypertension as reported here and elsewhere, it is difficult to concede that essential hypertension is due solely to arteriolar spasm. It is a physiologic principle that distal to a constriction of a lumen there is dilatation. During the course of the work here reported several cases of Raynaud's disease in which there is a true arteriolar spasm limited to the extremities were studied. Chilling of the hand causes a typical

TABLE 7.—RAYNAUD'S DISEASE.

Hospital No.	Case.	Temperature.	Capillary pressure, mm. Hg.	Venule pressure, mm. Hg.	Appearance of capillary.	Note.
186143	1	Warm	12	14	Large	
		Cold	5	5	No change	Cyanosed.
229166	2	Warm	...	8	Narrow	
		Cold	...	15	Dilated	Cyanosed.
		Cold	...	2	Dilated	Skin white after closing hand once.
276859	3	Warm	...	15	Large venous limb	
		Cold	...	5	No change	Skin dusky.
275909	4	Warm	10	15	Narrow	
		Cold	0	10	Dilated	Skin dusky.
251852	5	Warm	15	...	Narrow	
		Cold	5	...	No change	White hand.

attack, during which the capillaries at the nail base dilate and both the capillary and venule pressures fall. If essential hypertension is the result of an arteriolar spasm a similar type of reaction might be expected, even if not as intense. This was not found to be the case. The capillaries are narrow, especially their arterial limb, the flow of blood is normal or more rapid and the capillary and venule pressures are increased or near the upper limits of normal. This picture suggests that in essential hypertension there is a generalized constriction of the vascular tree.

The blood pressure of the capillary can vary independently of the rest of the vasomotor system. The capillary helps sustain the pressure head of the circulation by means of its contractile Rouget cells. It is sensitive to changes in oxygen content of the blood,[7] to variations in temperature and to chemical and mechanical stimulation. The pressure has been shown to be increased in some cases of hypertension,[1] frequently in acute and chronic nephritis[1,2,8,16] and the hypertensive toxemias of pregnancy.[2,9,10] It has been noted that the increase is associated with the active phase of the illness, the pressure returning to normal with convalescence; and the idea has become prevalent in the literature that the significant feature of these clinical conditions is a generalized capillary involvement.

In our work all the cases of acute nephritis had a high capillary pressure with blood and albumin in the urine, all disappearing in convalescence. A large majority of the cases of chronic nephritis with a high capillary pressure had albumin and blood in the urine. Furthermore, those with a marked hematuria were limited to the increased pressure group. This association of increased capillary pressure and urinary signs during the active stage of the disease is indicative of a systemic capillary involvement.[19] The significance of these findings may be clarified by a recent study[11] on the mammalian capillaries in the sartorius muscle. The typical reaction to any but harmful stimuli was dilatation. Vasoconstriction was the response to severe irritants which finally lead to endothelial destruction. In view of this statement the vasoconstriction or high capillary pressure found in the cases of nephritis suggests that there is a generalized stimulation of the capillary endothelium.

The capillary pressure is an indicator of the balance between the driving force of the bloodflow and the resistance of the vascular wall. The osmotic pressure is a measure of the attraction of the constituents of the blood serum for water. The endothelium is a semipermeable membrane of extreme thinness, being only slightly permeable to protein. Filtration of fluid from the blood to the tissue spaces takes place when the capillary pressure exceeds the osmotic pressure and resorption when the latter is greater. The rate of interchange depends upon the degree of difference in the two pressures. The normal capillary is the site of both these processes. Landis[4] has shown that in the arterial limb of the capillary the blood pressure exceeds the osmotic pressure, and that in the venous limb these relations are reversed. An exaggeration of this normal relationship, due either to an increase of capillary pressure or a decrease in osmotic pressure, will result in edema. When the endothelium is injured the rate of fluid loss is increased as much as four times.[7] This increase in permeability can be brought about by adding endothelial poisons to the blood or by deoxygenation of the experimental animal. To study the effects upon the human endothelium of a similar injury, patients in whom an intense anoxemia could be brought about were examined. When their oxygen administration was stopped cyanosis became intense, the capillary blood pressure fell abruptly and the rate of flow was reduced. With restoration of oxygen the pressure rose. Koranyi[12] believes that additional influences on the transudation of fluid are chemical and hormonal changes in the blood. Further, he feels that the protein content of the edema fluid slows the rate of flow through the capillary endothelium.

Clinically, the relationship of low osmotic pressure to edema has been emphasized first by Epstein[13] and others, but the rôle of the capillary pressure has been neglected. Cases are often seen in which edema is present with a normal serum osmotic pressure.

These exceptions were discussed in a recent paper[14] on edema and low serum protein, but in this case, too, the capillary pressure has been disregarded. Following the original conception of Starling, Krogh[15] and later Landis[7] have shown that changed values in both these pressures are requisite factors in loss of water from blood to tissue spaces. Two clinical studies have recently been reported confirming this. However, Nakazawa and Izumi[16] have calculated

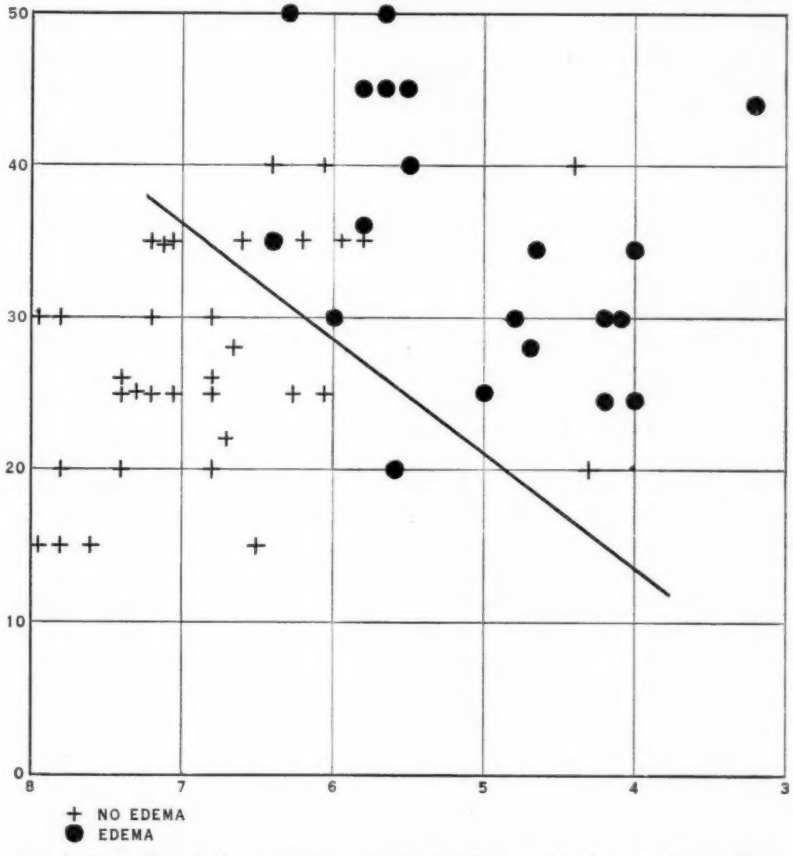

CHART II.—Relationship of capillary pressure and serum protein per cent to edema.

capillary pressures from that of the brachial artery. This is not a justifiable assumption, as in all the previous and present work it has been emphasized that there is no mathematical relationship between the two. In the work of von Farkas[17] the capillary pressure was calculated from the venous pressure. This method has not been found correct.[18] Von Farkas found the venous pressure normal in cases of nephritis with edema and high when there was an associated cardiac decompensation. However, Koranyi feels that in

spite of the low venous pressure the capillary pressure is higher than the osmotic pressure of the blood plasma.

An analysis of the cases with edema would indicate that the blood pressure of the capillary is an important factor. In the presence of a very high capillary pressure edema will result even though the osmotic pressure is normal or a low normal. To visualize the interrelationship of these two pressures to the presence or absence of edema all the cases reported in this paper have been plotted in Chart II. It shows the serum protein per cent on the abscissa and the capillary pressure on the ordinate. Study of this graph shows that the vast majority of the cases with edema group themselves in the upper right side; those without edema fall in the lower left side. A line can be drawn separating these well-defined groups, and it appears to lie just above an imaginary line which connects the points at which both the pressures are balanced and fluid interchange is at a standstill. There was only one marked exception in the nonedematous group; however, doubt was cast upon the accuracy of its serum protein, as on many subsequent examinations it was found to be normal.

In the cases associated with cardiac insufficiency both the arterial and venous limbs contribute to the formation of edema. The pressure is high in both, and not only is there increased fluid loss from the blood but delayed absorption from the tissue spaces.

Summary. 1. A comparison has been made between the capillary morphology found in essential hypertension and peripheral arteriolar spastic (Raynaud's) disease. From their marked difference it seems more probable that essential hypertension is due not solely to arteriolar spasm but to a generalized arterial spasm.

2. The frequent association of high capillary blood pressure with renal disease is indicative of a spasm response due to a severe involvement of the systemic capillary system.

3. A relationship between the capillary pressure and osmotic pressure of the blood to the presence of edema has been found to exist in nephritis.

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THE PRACTICAL APPLICATION OF THE BLOOD SEDIMENTATION TEST IN GENERAL MEDICINE.*

Observations Based Upon Approximately 5000 Patients Over a Period of Six Years.

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The blood sedimentation test is one of the newer laboratory procedures, striving for a place as a valuable diagnostic aid and prognostic index in infectious and other destructive diseases. It has been studied extensively in two fields of medicine, in pulmonary tuberculosis and gynecology. In these fields it has been accepted by many as a valuable addition to the armamentarium of the physician and as a more reliable source of information than some of the usually accepted procedures on which he customarily bases his judgment. Its importance as a routine procedure in general medicine and especially in office and dispensary practice has, however, received little if any consideration, and it is the purpose of this paper to describe some of its possibilities.

This paper is based on experience with the sedimentation test acquired through intensive study in hospital, dispensary, and office practice during the past 6 years. What I wish to present at the

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present time is a broad outline of this experience, based upon personal observations on more than 5000 patients, covering practically every common disease encountered in the practice of "internal medicine."

It is not within the scope of this discussion to consider the various hypotheses that have been suggested to explain the phenomenon of blood sedimentation. It is safe to say, however, that out of a host of explanations, whether in terms of autoagglutination, of electrophysical reaction, of increased fibrinogen content of blood plasma, or of a specific something (ferment) in the plasma, not one is generally accepted.

However, evidence is accumulating to show that essentially the sedimentation phenomenon depends upon the amount of cellular destruction going on in the body. As the blood circulates from part to part it carries away products of tissue destruction, which alter its stability. In healthy persons, as a result of the wear and tear of everyday life, a certain amount of tissue destruction is always taking place, and although this varies from day to day it remains within limits considered normal. Even this relatively small amount of tissue destruction is registered by the sedimentation test. This was clearly shown by Greisheimer,[1] who made 174 repeated observations on a group of 31 healthy men and women and observed that the sedimentation rate varied from week to week in the same individual, but always within normal limits.

Should the amount of tissue destruction pass beyond the normal, then the stability of the blood is seriously disturbed and the red blood cells settle out quickly from the plasma. All the observations recorded in recent literature emphasize this important fact: that regardless of the disease present, whether it be active pulmonary tuberculosis, malignancy, pelvic inflammatory disease, and acute infections such as typhoid fever, or any disease in which tissue destruction is going on at a greater pace than normal, the rapidity of settling of the red blood cells is in direct proportion to the severity of the disease.

It is evident, therefore, that the sedimentation reaction portrays a disturbed physiology of the blood resulting from a destructive process, and should be looked upon as one of the fundamental phenomena occurring during disease and regarded as an indication and measure of pathologic activity in the same sense as fever or leukocytosis.

Technique. The 1 cc. Cutler graphic technique was followed throughout. This technique is very simple and can be carried out by the physician in his office without difficulty.[2] The essential features are as follows:

Specially designed sedimentation tubes of 1 cc. capacity are used, graduated into 50 mm. divisions, with 0 at the 1 cc. level; each millimeter indicating 0.02 of 1 cc. One-tenth of 1 cc. of a

3 per cent sodium citrate solution and 0.9 cc. of blood, obtained by puncture of a suitable vein, are gently mixed in a 2 cc. syringe and poured into the sedimentation tube. The position of the sedimenting column of erythrocytes is determined every 5 minutes for 1 hour (Fig. 1). The observations are recorded on charts that have been designed for the purpose, on which the horizontal lines represent the divisions on the tube and the vertical lines the intervals of time. Graphs are then constructed, which not only show the position of

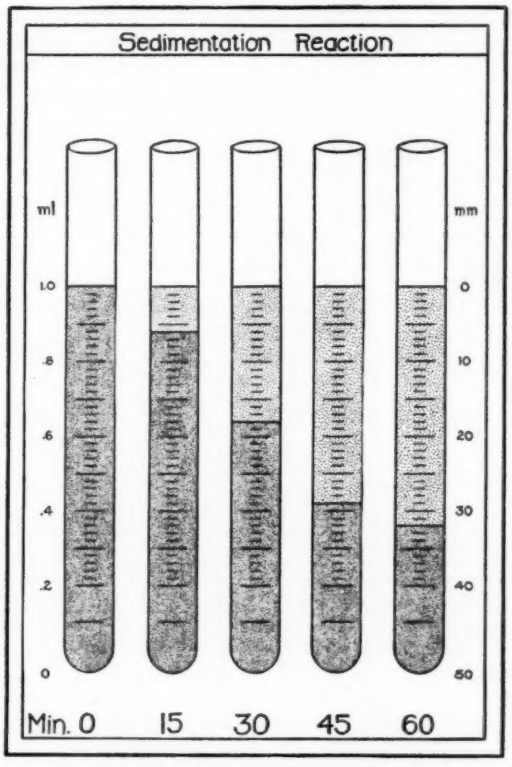

FIG. 1.—Blood sedimentation at different time intervals in a patient with rapid settling of the red blood cells (pelvic inflammatory disease.)

the sedimenting column of erythrocytes at any period of time during the first hour, but also portray the changes in velocity that occur during the process of sedimentation (Fig. 2).

Four distinct graphs are recognized, a horizontal line, a diagonal line, a diagonal curve, and a vertical curve. Of these, the horizontal line alone is normal, the other three graphs are always abnormal findings and always indicate different degrees of the intensity of the

NOTE.—The sedimentation tubes may be obtained from Arthur H. Thomas Co., Philadelphia, the charts from John Hartenstine, Norristown.

destructive process. For greater detail the reader is referred to previous communications.[3,4]

Test Studied Under Three Headings. With this introduction let us see what the sedimentation test has to offer the busy physician when used as a routine procedure in everyday practice. It seems best, in order to avoid confusion, to discuss the test under three headings: First, its diagnostic value; second, its value in prognosis and as a therapeutic guide, and third, its limitations.

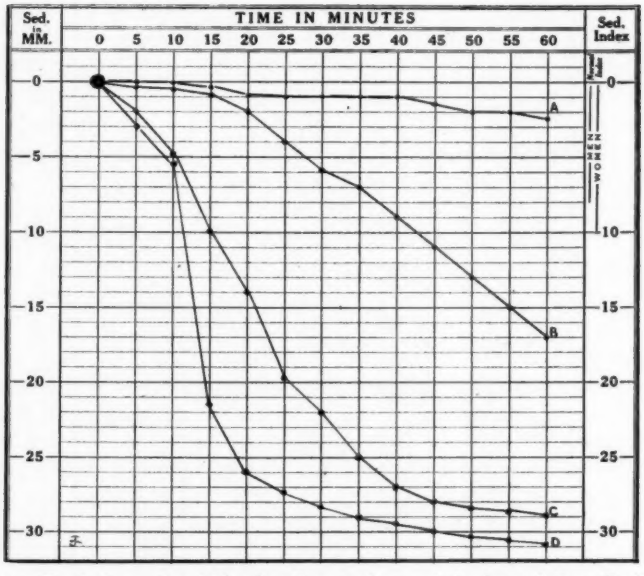

FIG. 2.—Typical graphs of blood sedimentation. *A*, horizontal line; *B*, diagonal line; *C*, diagonal curve; *D*, vertical curve. Of these the horizontal line alone is normal; the other graphs are always abnormal and indicate different degrees of the severity of the disease.

The Diagnostic Value of the Sedimentation Test. The sedimentation test is nonspecific and is not a procedure for diagnosing any particular disease (Fig. 3), but rather as a general symptom like fever and leukocytosis. As such, it serves as a valuable diagnostic aid in two ways: First, as a *lead* in diagnosis, indicating the presence of noteworthy disease, not infrequently before it is manifest clinically; and second, as a *measure* of the intensity of the disease process, often more accurately than the more commonly accepted procedures.

The sedimentation test is perhaps most useful as a diagnostic lead. A careful review of a reasonable number of records in any well conducted dispensary or office will readily convince one of the value of some simple laboratory procedure that can by a single determination indicate the presence of serious disease and distinguish the seriously ill from the patient with symptoms of minor

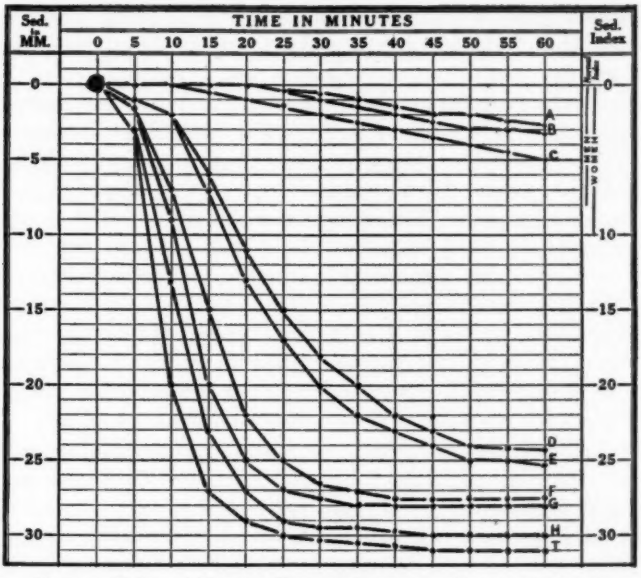

FIG. 3.—Nonspecificity of blood sedimentation test. Almost identical graphs are obtained in widely different diseases. *D*, pulmonary tuberculosis; *E*, bronchiectasis; *F*, lobar pneumonia; *G*, chronic bronchopneumonia; *H*, lung abscess; *I*, carcinoma of lung; *A*, *B* and *C* show indifference of test to pathologic conditions of noninfectious nature. The patients suffered with asthma, mitral stenosis and chronic sinusitis respectively.

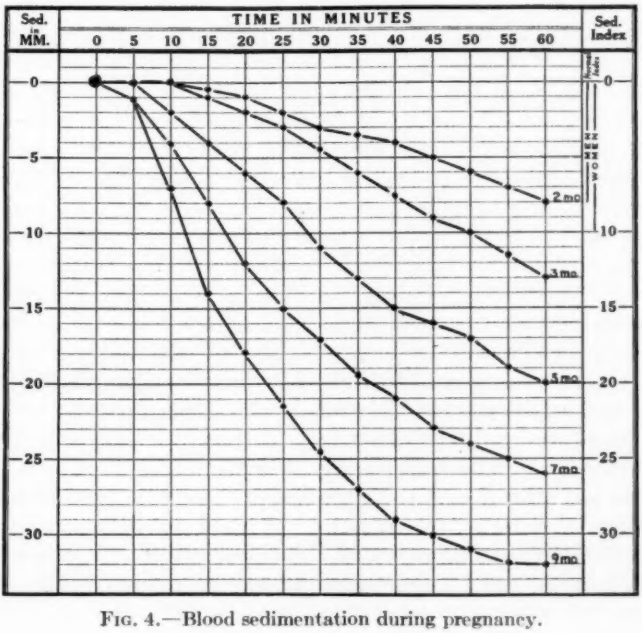

FIG. 4.—Blood sedimentation during pregnancy.

significance. Such a test would undoubtedly be of inestimable value in helping the physician arrive at an accurate diagnosis earlier and in a larger number of patients than is now possible.

In the sedimentation test we have just such a procedure. Increased settling of red blood cells, as far as we know today, occurs when there is increased destruction of tissue and, therefore, rapid sedimentation demands explanation in terms of disease and should never be disregarded. Pregnancy is the only physiologic process that is accompanied by rapid sedimentation (Fig. 4).

In a series of more than 1000 cases observed consecutively at the Henry Phipps Institute, 328 patients were diagnosed either as apparently healthy or suffering from some trivial and transient symptoms of slight pathologic importance. The diagnosis was based upon careful history and physical examination, with the usual observations as to pulse, temperature and weight. Of this number 177 (54 per cent) had a definitely abnormal sedimentation rate for which no satisfactory explanation could be given by the examining physician. When these patients, however, were subjected to routine Roentgen ray examinations of the chest, Wassermann tests, nose and throat examinations, and the women to routine gynecologic examinations, the abnormal sedimentation test no longer remained a mystery. In 96, basal infiltration of the lungs of varying extent and nontuberculous in character were found by Roentgen ray. In 32 the Roentgen ray revealed latent tuberculosis involving the apices. Positive Wassermann and Kahn reactions were found in 35. In 5 women the gynecologist made a diagnosis of pelvic inflammatory disease and recommended operation. In 1 carcinoma of the lung was suspected because of Roentgen ray findings. In 8 no definite pathology could be demonstrated but there was sufficient reason to warrant holding these patients for further observation. Thus in most of these cases the significance of the abnormal sedimentation rates was explained by the final diagnoses. These patients had either trivial symptoms or no symptoms at all. In every instance a careful physical examination by a competent physician was negative and a tentative diagnosis was made of "apparently healthy." This is particularly striking in the group of patients with significant Roentgen ray findings in the lungs, for the physicians who made the physical examinations of the chest were especially trained to recognize the early signs of disease and might properly be called "chest specialists."

The abnormal sedimentation rate in these patients undoubtedly served as a diagnostic lead, clearly indicating that in spite of negative signs and the absence of symptoms the patient was not healthy but harbored some serious ailment. If these patients had not been subjected to a painstaking search, no satisfactory explanation could have been advanced for the abnormal sedimentation and superficial criticism would have branded the test as "unreliable."

The following are typical specific instances in which the sedimentation test was or might have been of definite help as a diagnostic lead:

A woman, who was studied in different hospitals, had gall bladder symptoms and was then diagnosed as neurasthenic. Her sedimentation was active. An operation revealed carcinoma of the head of the pancreas.

A woman, with loss of weight, was told she had cancer. Her sedimentation was normal. An operation showed adherent gall bladder, and was followed by complete recovery.

A woman, with suppurative bronchitis, had had a diagnosis of nervous cough, which was contraindicated by an abnormal sedimentation rate.

A woman, with vague symptoms and a family history of tuberculosis, was apparently in good health and told to go to work. Her sedimentation rate was abnormal. She gave a positive Wassermann reaction.

Classifying the different diseases studied according to whether or not they cause increased settling of the red blood cells, we can group them under three headings.

TABLE 1.—DISEASES GROUPED ACCORDING TO SEDIMENTATION RATES.

With an Abnormal Sedimentation Rate.

1. Chronic infectious diseases, such as tuberculosis and syphilis.
2. Acute infectious diseases, such as pneumonia, septicemia, acute endocarditis, the exanthemata and acute bronchitis.
3. Malignancy.
4. Localized suppurations, such as pelvic inflammatory disease, suppurative mastoiditis, suppurative sinusitis, empyema of the gall bladder, bronchiectasis.
5. Acute intoxications, such as lead and arsenic poisoning.
6. Certain endocrine disturbances, such as thyroid toxicosis.

Influencing the Sedimentation Rate Very Little If At All.

1. Simple catarrhal inflammations, such as acute catarrhal appendicitis, simple rhinitis and colitis.
2. Chronic ulcerations of small extent, such as gastric or duodenal ulcer.

Not Influencing the Sedimentation Rate.

1. Functional diseases, such as the various neuroses, and neurasthenia.
2. Certain nervous diseases, such as dementia precox.
3. Focal infections, such as abscessed teeth, diseased tonsils and chronic sinusitis.
4. Metabolic diseases, such as uncomplicated diabetes and essential hypertension.
5. Allergic diseases, such as asthma and hay fever.
6. Most skin diseases.
7. Simple growths, such as fibroma, lipoma and fibromyoma.
8. Simple cysts.
9. Chronic valvular disease of the heart.

Rapid sedimentation, in other words, is found only in infectious disease and malignancy.

It must be clearly understood that a normal sedimentation reaction does not rule out serious disease. For instance, patients may harbor advanced tuberculosis and still have a normal sedimentation

rate. In such cases the normal reading indicates that the tuberculosis is not active, or at least there is not sufficient tissue destruction to cause increased settling of the red blood cells.

To state the same thing in another way—a normal sedimentation reaction indicates one of two things, either health or the existence of destructive disease, not sufficiently active to disturb the natural stability of the blood; an increased sedimentation reaction is always abnormal, and except in pregnancy indicates the presence of disease.

We have then in the sedimentation test a sensitive method for detecting serious disease as soon as it becomes sufficiently active to disturb the stability of the blood.

The Value of the Sedimentation Test as a Prognostic and Therapeutic Guide. The second use to which the test readily lends itself in diagnosis is its ability to evaluate in definite terms the degree of constitutional disturbance produced by the pathologic process. No diagnosis of any disease can be said to be complete without such knowledge and the skillful physician employs every aid of his profession to obtain this knowledge. It is only after an accurate and considerate estimation of the intensity of the disease process that intelligent treatment can be planned. Its importance to the welfare of the patient from a practical sense can hardly be overstated.

The ability of the sedimentation test to supply this information more accurately than most of our usually accepted procedures, such as temperature curve and pulse rate, blood count, or physical signs and symptoms, was one of its first characteristics to be recognized clinically and wide use has been made of it in tuberculosis and gynecology, in the former to indicate the activity of the tuberculous process and in the latter the safe time for operation in pelvic inflammatory disease. This aspect, its usefulness as a quantitative index, has been emphasized in many excellent contributions to the literature on the subject.

As a measure of constitutional disturbance the sedimentation test may clearly be of great value to everyday clinical practice, not only in diagnosis but also in prognosis, and as a guide to treatment. The changes in sedimentation rate parallel the severity of the disease, becoming more rapid as the disease becomes worse and slowing down to normal as the condition of the patient improves.

The graphs of subsequent sedimentation findings recorded upon the original chart is a dramatic and convincing indication of the progress of the disease in terms of constitutional disturbance, unequalled by any existing clinical or laboratory method for its accuracy and simplicity. It is not subject to psychologic influences or to the promises of a well-meaning physician or pharmaceutical house; if the treatment has no direct effect upon the disease, sedimentation will continue rapid. At times it may even increase in rapidity in the face of apparent symptomatic improvement and well-being.

Clinical Examples.—CASE 1.—A most striking example was observed in J. R., aged 67 years, who was first seen on December 3, 1929. One month later a diagnosis of carcinoma of the right bronchus was established through biopsy. The patient died 9 months later and had clinical manifestations of metastasis several months before death. About 6 months before he died he seemed to have improved clinically to such an extent that the family and the patient became unusually hopeful. His symptoms of cough and expectoration became less, pain was less marked and his strength improved. He even gained a few pounds in weight. As a coincidence his treatment at that time consisted of 5 cc. of a 5 per cent solution of calcium chlorid, given intravenously twice weekly, in addition to the usual supportive measures. The family was convinced that the patient was getting better and that the improvement was due to the intravenous medication. As can be seen from the graphs *C* and *D* (Fig. 5) sedimenta-

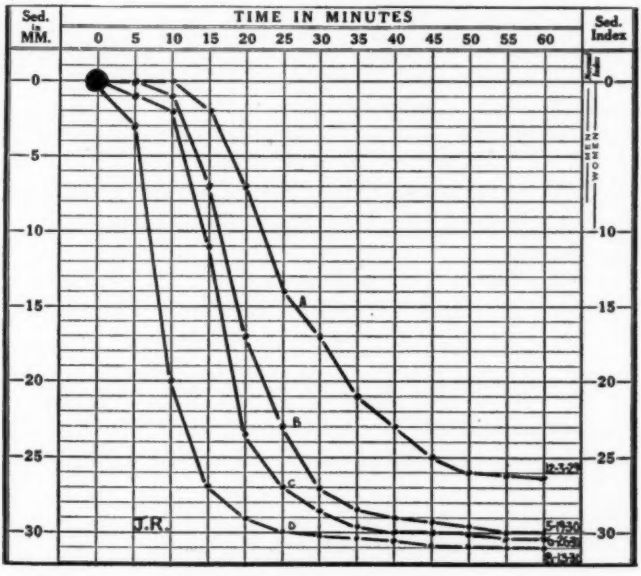

FIG. 5.—Blood sedimentation in fatal carcinoma of the lung.

tion during this period of symptomatic improvement became more rapid and continued to increase in rapidity until death. The sedimentation was not influenced by mental phenomena but remained a true guide to the severity of the malignant process and prevented the indulgence of false hopes.

A few typical examples and the accompanying figures further illustrate the usefulness of the test in prognosis and in guiding treatment.

CASE 2.—S. S., aged 23 years, was admitted to the Northern Liberties Hospital on December 19, 1929, with acute pulmonary tuberculosis involving the right upper lobe and complicated by severe hemoptysis. Artificial pneumothorax was instituted, December 21, and the patient responded well. He was discharged in good condition and practically free of symptoms

thirty days later, to continue his pneumothorax treatments in the clinic. His recovery has been uneventful and at the present time he is pursuing an active life. Fig. 6 depicts the daily variations in temperature during his

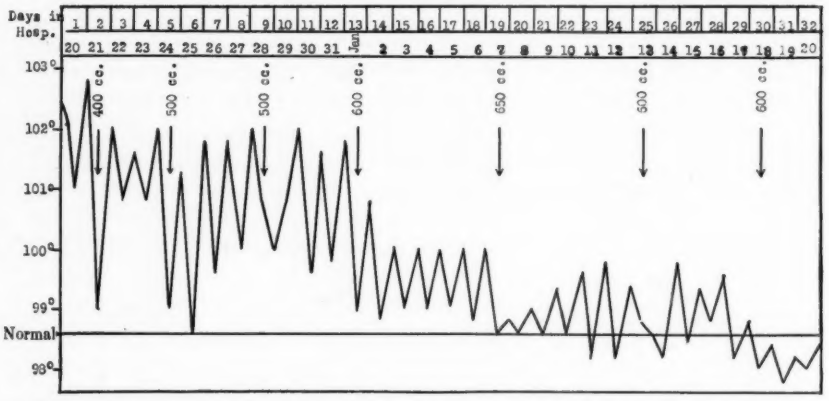

FIG. 6.—Daily temperature curve in a case of acute tuberculosis treated by artificial pneumothorax (indicated by arrow).

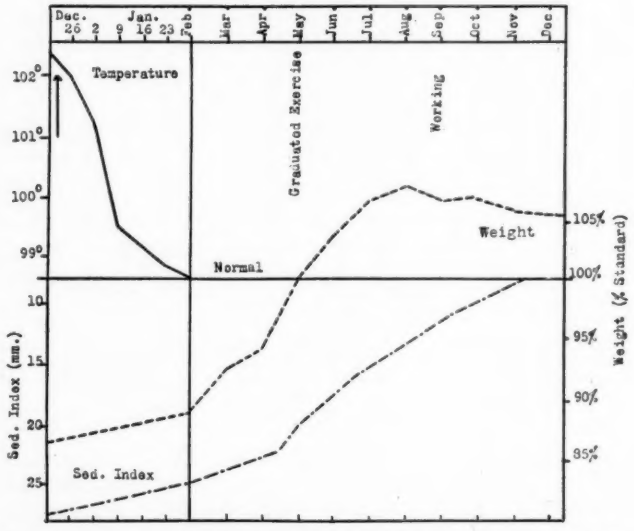

FIG. 7.—Clinical course during the first year of treatment by artificial pneumothorax illustrating the relative rapidity with which the temperature, weight and sedimentation rate returned to normal. The temperature as a representative symptom of toxemia was the first to subside. The sedimentation rate, on the other hand, did not recover until 9 months after the temperature and other signs of toxemia were absent. The vertical line denotes a change in scale from weeks to months. (Same patient as in Fig. 6.)

stay in the hospital. Fig. 7 illustrates the clinical course during the first year that the patient had been under observation and indicates the relative rapidity with which the temperature, weight and sedimentation rate returned to normal.

The temperature as a representative symptom of toxemia was the first to subside. The sedimentation rate, on the other hand, did not recover until 9 months after the temperature was normal and the signs of toxemia absent. It was the last objective observation to return to normal and for months was the only indication of the pathologic state of the compressed lung.

Fig. 8 illustrates the course of the sedimentation graph observed during the first year of treatment as recorded on one chart and shows what an excellent method we have here for visualizing steady improvement in favorable cases. The shaded area of the chart indicates the sedimentation graphs obtained during the absence of clinical signs and symptoms, at a time when something was desperately needed to indicate the true state of

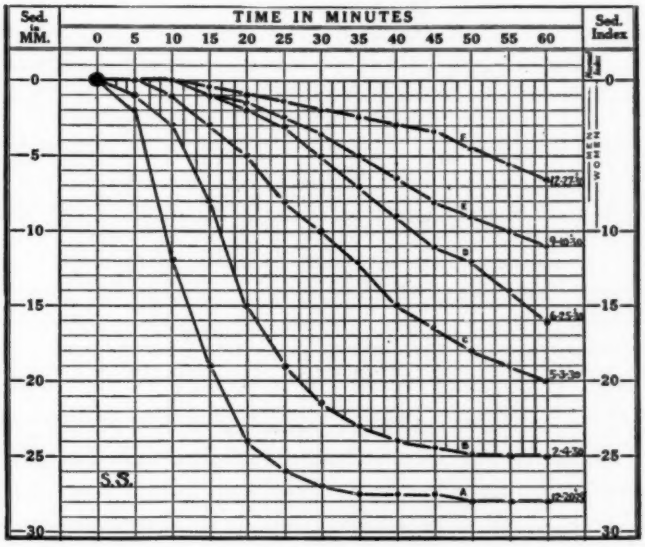

FIG. 8.—Sedimentation graphs obtained during first year of treatment by artificial pneumothorax. The shaded area indicates the sedimentation graphs obtained during the absence of clinical signs and symptoms. (Same patient as in Figs. 6 and 7.)

affairs in the compressed lung. Without the sedimentation test the clinical management of this case would have been much more difficult.

When the disease is not responding to treatment the sedimentation test will either remain fixed or increase in rapidity.

CASE 3.—F. P., aged 24 years, first came under observation for advanced pulmonary tuberculosis involving the left lung in February, 1930, when artificial pneumothorax was started. She has been under treatment ever since. Unfortunately the cavities in the left lung can be compressed very slowly and with great difficulty because of the adhesions and, although clinically she is comfortable, there has been little if any improvement in the sedimentation rate over a period of 1 year. Fig. 9 illustrates some of the graphs observed during this period in this patient, and is very convincing proof of the lack of actual improvement in the lung.

Fig. 10 illustrates the steady increase in rapidity of sedimentation in a patient with bilateral tuberculosis who at first responded remarkably well to artificial pneumothorax and then suffered a spread in the right or "good" lung. The spread was rather extensive, and at first gave no warning clinical signs or symptoms. It was only because of the unexplained increases in the rapidity of the sedimentation rate that the true state of affairs was

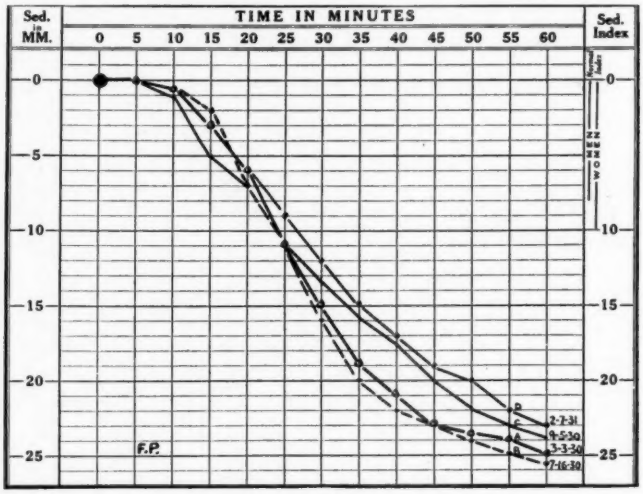

Fig. 9.—Sedimentation graphs obtained during the course of chronic pulmonary tuberculosis treated by artificial pneumothorax but with little or no improvement.

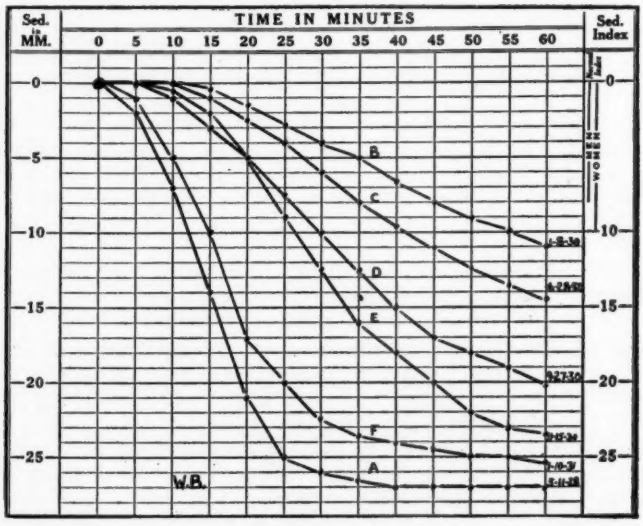

Fig. 10.—Sedimentation graphs obtained during the course of chronic pulmonary tuberculosis treated by artificial pneumothorax with spread in the untreated or "good" lung. *A*, before treatment was started; *B*, nineteen months later (patient free of symptoms and able to do a full day's work); *C*, *D*, *E*, *F*, increased sedimentation accompanied by extensive spread in right or "good" lung with cavity formation. Patient ordered back to bed at *D*.

quickly recognized and the patient ordered back to bed. Even to this day, although we know that there is advanced disease in the "good" lung, as revealed by Roentgen ray and fluoroscopic study, one can detect very few if any definite physical signs. The patient is free of fever and cough and has only slight expectoration in the morning. He is overweight and feels well in every respect. The unexplained increase in sedimentation rate, determined as part of routine practice in the management of such cases, serves, like a storm signal in a calm, as a warning that trouble has begun, and that it is no less real because it is not yet visible.

Other striking examples of the usefulness of the sedimentation test as a check upon therapeutic measures are shown in the accompanying illustrations. Some of the cases have been described in detail and others are sufficiently explained by the legends. Space forbids further discussion of interesting examples. The reader will find that the literature is rich in contributions on this phase of the subject, but best of all he can find his own examples through clinical trial at the bedside.

Limitations of the Sedimentation Test. The author is well aware that much criticism will be directed against this test, if for no other reason than because the claims made for it are of such fundamental importance as to challenge the imagination. No doubt some will argue that if what is claimed is true then all that one will have to do in the future to know anything desired about the state of the patient is to perform a sedimentation test. On the other hand, others will see no value in it at all. They will argue that the sedimentation test is merely another addition to the laboratory playhouse—interesting but not essential. If the physician will study his patient carefully and employ every method at his command at present, he will not need this new trick to tell him if his patient is ill, what to do for him or what the outcome will be.

These criticisms are heard many times. One can only reconcile oneself with the observation that it is in the nature of things for anything new to be challenged. Anything that stirs our stagnation and forces us to change our habits of thought and action is almost sure to be looked upon by some with suspicion and even regarded as an offence.

The sedimentation test is not a substitute for any existing clinical or laboratory procedure. On the contrary, it is complementary to them, and therefore essential, because it fills certain important gaps left by current methods. Although at first it may seem a luxury, repeated use at the bedside will soon establish it as a real necessity.

The sedimentation test will not make a good doctor out of a poor one, but it will undoubtedly make a keener and better physician out of a good one. The physician and not the test must determine the nature of the pathologic condition it points out to him. The test has served its purpose in diagnosis when it has indicated the existence of disease and thus warned the physician to make an unremitting search for the source of the disturbance. Once the diagnosis has been established the rate of sedimentation becomes a

measure of the intensity of the disease, more accurately than our commonly accepted procedures, and serves as a record of the response to treatment. It is obvious, therefore, that the sedimentation test has a field of usefulness of its own, not readily covered by existing laboratory and clinical methods. When we learn to look upon the increased rapidity of the settling of red blood cells as a measure of tissue destruction regardless of etiology, we shall have begun properly to interpret the test. We shall then begin to see the possibilities of its routine use in office, hospital and clinic.

The sedimentation test has certain real limitations which should be borne in mind: (1) It does not give a diagnosis of a specific disease. Neither does fever, nor leukocytosis. (2) A normal sedimentation is not conclusive evidence that there is no disease, but it does show that disease, if present, is producing very little if any constitutional disturbance. (3) Abnormal sedimentation reveals pathologic processes that cause tissue destruction, but these include the infectious diseases and malignancy. (4) Sedimentation is abnormally rapid with pregnancy after the third month. (5) The test is not infallible. I have seen a few instances and some have been brought to my attention of a normal sedimentation rate with clinically active disease. These cases are very rare and the reasons for them obscure. I recall only 5 in over 5000 observations. When we know more about the mechanism involved these exceptions may take on a meaning of their own. It is also true that not every abnormal sedimentation can always be explained in terms of disease, but such cases should be regarded as suspicious until proved otherwise.

Summary. The blood sedimentation test has been studied in hospital, office and dispensary practice during the past 6 years with more than 5000 patients. The test was found to be of distinct diagnostic and prognostic value in diseases characterized by disturbed stability of the blood. A list of such diseases has been drawn up, but consideration of the value of the test in any given disease has been reserved for separate communications. The present purpose is to describe and illustrate the fundamental characters of the sedimentation test in disease in general.

In diagnosis the test has two values, first as a diagnostic *lead* and the second as a diagnostic *gauge*. As a diagnostic lead it indicates the presence of serious disease, not infrequently before the disease can be recognized by the usual clinical and laboratory methods. As a gauge of the constitutional disturbance produced by the pathologic process, it indicates the intensity of the disease and thus, like fever or pulse rate or blood count, but more exactly, helps to complete the diagnosis in a qualitative sense.

As a prognostic index and, similarly, as a guide in treatment, the rate of sedimentation has been shown to be a more accurate and reliable reflection of the real condition of the patient than our usually accepted procedures. It invariably becomes more rapid as the

disease progresses, and approaches stability only as the physical condition returns to normal. It is not influenced by psychologic factors and may be the only warning of disaster among promising clinical signs, such as gain in weight and the absence or subsidence of symptoms. In this way it is often the only, or the most accurate, evidence of favorable, or of unfavorable, response to treatment.

The test is very simple to perform and to interpret and is inexpensive. It is a clinical procedure and can be carried out in the office, in the dispensary or at the bedside. The complete result is available within an hour and in case of necessity the sedimentation test will give valuable information within the first half hour.

Its greatest field of usefulness should be in office and dispensary practice, especially in the latter, where large numbers of patients must often be seen in short periods of time and by men seeking experience. Properly interpreted and used with an open mind, the test should in time become one of the most widely used tests in clinical medicine.

Its practical value in any given disease is best studied as a separate problem and such studies should be undertaken in large numbers so that sufficient data become available in a short period of time. Only in this way will lingering doubts be removed and the sedimentation test firmly established as a valuable addition to the equipment of the physician.

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PATHOLOGIC CHANGES OCCURRING IN POLYMORPHONUCLEAR LEUKOCYTES DURING THE PROGRESS OF INFECTIONS.

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The response of the blood-forming organs to infections is influenced by the type of the invading organism and the intensity and extent of the infection. Ordinarily, pathogenic organisms call

forth a leukocytosis and a polynucleosis, while certain forms of obscure infection are followed by a lymphoid or monocytic response. In some infections, notably subacute bacterial endocarditis, macrophages may appear in the peripheral blood. In trichinosis the main reaction is shared by the eosinophils. Leukocytosis and polynucleosis may be absent in infectious conditions which are more or less severe. In such instances the ordinary blood examination may be insufficient and misleading, while attention to certain other details of the individual cell, such as nuclear and cytoplasmic changes, may indicate the presence of an underlying bacterial infection.

In addition to the value of the white and differential count, this paper is intended to show the significance of the nuclear and cytoplasmic changes in the granulocytes which occur in certain infections because these have a diagnostic and prognostic importance. Realizing the need for more detailed methods of examination, Arneth,[1] in 1904, proposed a subdivision of the leukocytes into various types. He showed that the main response to infection occurred in granulocytes which had one or two lobules to the nucleus. Kothe[2] and Türk[3] suggested further simplification of the method of counting polymorphonuclear cells by dividing them into lobulated and nonlobulated cells. The value of this modification of the Arneth count has been emphasized by Pons and Krumbhaar,[4] who divided the polymorphonuclear leukocytes into segmented (or older cells) and nonsegmented (or younger cells). Recently Farley[5] introduced filament and nonfilament count, corresponding to the segmented and nonsegmented polymorphonuclear cells. Schilling modified the Arneth method and classified the polymorphonuclear cells into three groups: (1) *Young cells, or metamyelocytes,* which are not present in normal blood and which usually have a short, broad, reticulated nucleus; (2) *the staff or band form,* which shows a thinner nucleus, somewhat irregular in shape; (3) the *segmented polymorphonuclear cell,* in which the nucleus is lobulated and the lobules are joined to one another by a definitely formed thread. It is often difficult to distinguish between the young cells and the band form, and it would not detract from the value of the hemogram to combine the two types of cells, according to the methods of Kothe or of Pons and Krumbhaar.

The diagnostic importance of the increase of the nonsegmented polymorphonuclear cells cannot be overestimated. An increase of these cells or shift to the left (toward the staff type) in a series of blood examinations usually is indicative of severe infection. The greater the number of nonlobulated cells above the normal (average normal is 5), the more extreme is the degree of infection.

Previous observers have noted cytoplasmic as well as nuclear changes in the granulocytes. Such cytoplasmic changes are large, irregular, basophilic alterations of neutrophilic granules. Cesaris-

Demel[7] (1908), employing supravital stains in studying the leukocytes, reported the finding of marked albuminoid and fatty granular changes. Schleip[8] noticed denser granules in the polymorphonuclear cells in leukocytosis. We are indebted to Türk[3] for the first complete description of the "toxic degenerative" changes in the granulocytes during severe infections. Naegeli,[9] Alder[10] and, especially, Gloor[11] paid particular attention to the prognostic importance of the granulocytes with "toxic" granules. Special stains for the identification of these granules were devised by Freyfeld[12] and Mommsen;[13] the latter investigator showed that blood smears stained with Giemsa (diluted with a buffered solution of pH 5.4) colored normal granules rather weakly in contrast to the "toxic" granules. More recently Varga[14] called attention to the presence of two types of granules—large in the febrile stage and small in the convalescent stage. This writer found no direct relationship between the Schilling hemogram and "toxic" granules. These granules are present with either hyperleukocytosis or leukopenia. In contradistinction to the theory that "toxic" granules are the result of histologic degenerative change (Schilling[15]) or to a toxic effect associated with suppuration (Naegeli,[9] Gloor[11]), Barta[17] has lately suggested that they are phagocytosed particles.

Methods of Demonstrating Toxic Degenerative Cells. Inasmuch as the value of any laboratory method depends directly upon its accuracy and its simplicity, we have, after trying various stains and methods, finally used our routine Jenner-Giemsa* stain, maintaining the water at a pH of 6.4 to 7. This method consumes only 15 minutes and gives blood pictures which are adapted to minute study of the normal as well as the pathologic changes in the individual cell.

Control smears from normal blood should always be made. This is done by using the outer third of the slide for the normal smear and making it at an angle so as to distinguish it from the patient's blood on the same glass slide. In this manner the staining quality of the patient's granulocytes can be readily compared with the normal.

Degenerative Cytoplasmic Changes. The *normal* polymorphonuclear neutrophil, when stained with the Wright or preferably with the Jenner-Giemsa stain, is usually a round cell, more than twice the size of a red cell. The cytoplasm shows a pinkish tint, and the nucleus is of a purplish-violet color, its outline being sharply defined. (Fig. 1.)

* Blood smears are covered with Jenner's stain for 1 minute, and then diluted with distilled water at a pH of 6.4 to 7 for 3 minutes. Distilled water can be brought to proper pH by adding 3 cc. of N/15 Na_2HPO_4 to 1000 cc. of distilled water. The slide is then tilted to remove diluted Jenner, washed once with buffer solution and Giemsa solution added (1 drop to 1 cc. buffer solution) for 10 minutes. The slide is then washed and dried. Wright stain may also be used with the same buffer solution to identify "toxic" granules.

The *abnormal or degenerative* polymorphonuclear neutrophil, on the other hand, presents certain striking histologic changes. The cell outline has a tendency to be irregular, and at times presents a moth-eaten appearance. The cells also vary in size in a manner analogous to anisocytosis of the red blood cells. (Fig. 2.) There are found in a few cells projections of clear bluish cytoplasm suggestive of pseudopodia. The fine neutrophilic granules are replaced by large, dark, irregular, basophilic granules which may fill the entire cell. (Fig. 3.) These granules may be free from or may be associated with changes in the cytoplasm, such as the presence of irregular bluish clumps (Doehle bodies) or a diffuse bluish cytoplasm found in myeloblasts. Further evidence of degeneration is shown in the presence of vacuoles, sometimes few in number and at times occupying most of the cytoplasmic area. These vacuoles may be present in a cell without the accompanying basophilic granular changes. It must be emphasized that the pathologic changes in the cytoplasm of the degenerative cells were found to be equally great in the younger and immature polymorphonuclear leukocyte as in the mature segmented forms, *i. e.*, they were not dependent upon the age of the cell.

Nuclear changes such as were described by Arneth and, later, by Schilling, were noted by us. These alterations are usually indicative of active regeneration; they can also occur in noninfectious conditions, such as hemorrhage, excessive exercise and following surgical operations.

Modified Hemogram. The counting and differentiating of these cells may be simplified by the use of a modification of the Schilling hemogram. (Table I.)

TABLE 1.—MODIFIED HEMOGRAM.

PATIENT: Baby S. WARD X DATE: 1-10-31
DIAGNOSIS: Pneumonia.
HEMOGLOBIN: 65 per cent
RED CELLS: 5,010,000
PLATELETS: 320,100
LEUKOCYTES: 5100

DIFFERENTIAL COUNT:	Total, per cent.	Normal.	"Toxic."
Polymorphonuclears, nonsegmented	73	0	73
Polymorphonuclears, segmented	15	0	15
Polymorphonuclear eosinophils	0	Degenerative index:	
Polymorphonuclear basophils	0	(88 ÷ 88) − 100	
Lymphocytes	15	Clinical data:	
Monocytes	13	Bronchopneumonia, 11th day; temperature, 105°F.	
OTHER CELLS:			
Myelocyte neutrophils	3		
Myeloblasts	6		

It became obvious at the outset that the degenerated cells are associated with infections. A single determination of the presence of degenerated cells, though helpful, is not sufficient. Serial observations should be made during the course of an infection. Our main purpose in using the hemogram was to obtain a quanti-

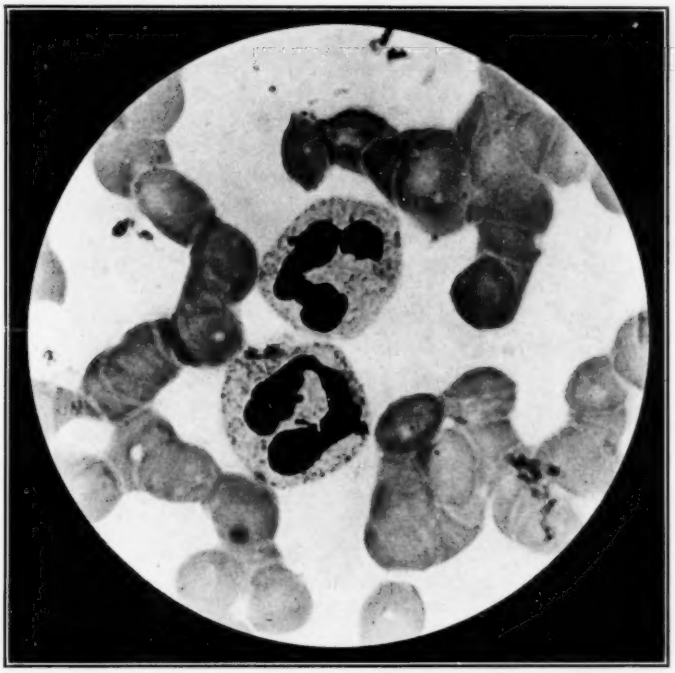

FIG. 1.—Appearance of polymorphonuclear neutrophils with Jenner-Giemsa stain in a normal control smear. Note the absence of "toxic" granules.

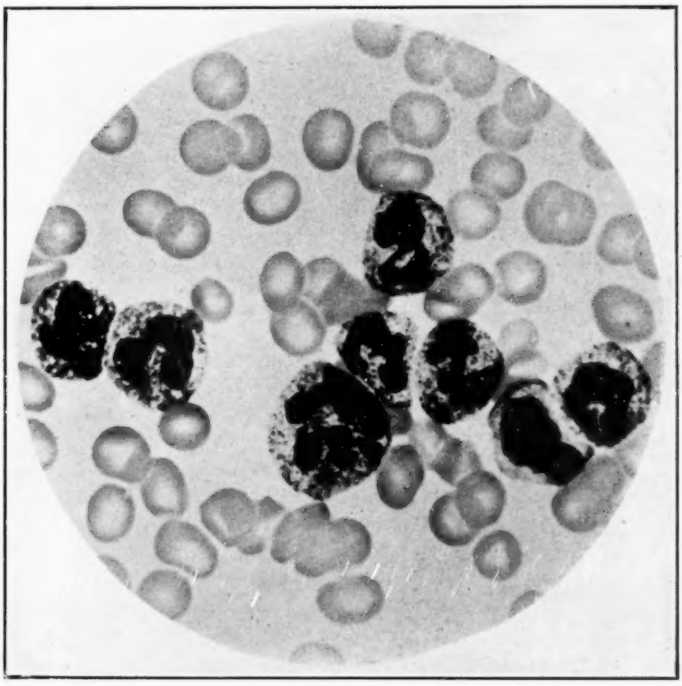

FIG. 2.—Acute lobar pneumonia (Jenner-Giemsa stain). "Toxic" granules in all segmented and nonsegmented polymorphonuclear neutrophils. Note anisocytosis of the leukocytes and also large polymorphonuclear neutrophils.

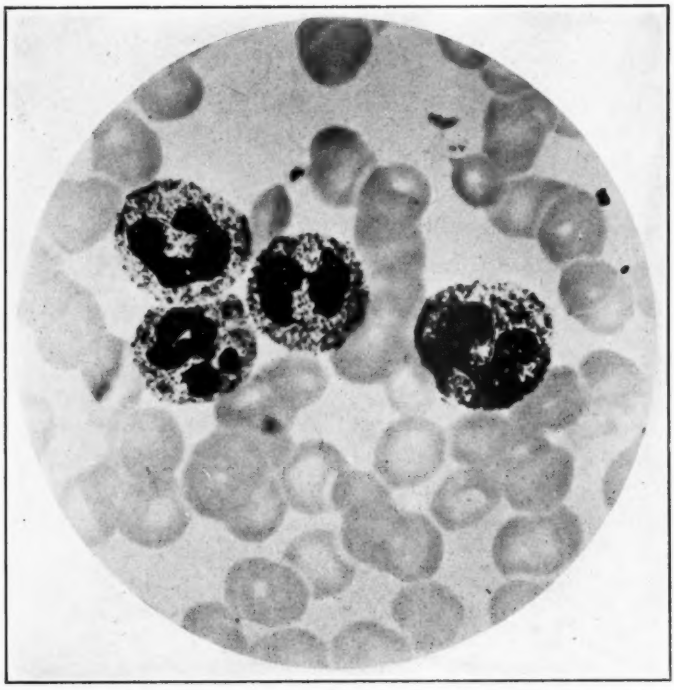

FIG. 3.—Acute lobar pneumonia, convalescent stage (Jenner-Giemsa stain). Note variations and staining intensity of "toxic" granules in the segmented and non-segmented polymorphonuclear neutrophils.

tative estimate of the number of degenerated cells. The percentage of pathologic cells may be estimated by dividing the number of degenerated polymorphonuclear leukocytes by the total number of polymorphonuclear leukocytes. This may be regarded as a *degenerative index*. Mommsen[13] reported the variations in the number of degenerated cells in certain infections, and found a rise in the number of these "toxic" cells during the disease and a diminution during convalescence.

The study of infections with the use of the modified hemogram proved to be of practical importance. Over 100 cases showing various degrees of infection were studied. The cases studied may be divided into the following four definite groups:

1. *Normal Controls.* Numerous controls were always made in normal individuals, as a check upon the proper staining of the cells. Degenerative polymorphonuclear cells were rarely found; possibly one or two cells showed cytoplasmic changes. The degenerative index was always approximately 0. The variation of the nonsegmented polymorphonuclear neutrophil usually ranges from 1 to 10 per cent.

2. *Nonsuppurative Conditions Showing Leukocytosis.* Eight typical cases were studied. Bleeding or operation was the basic cause of a polynucleosis. Nonsegmented (or staff) cells were increased in 4 of the cases (14 to 46 per cent). Degenerative changes, however, were lacking. The total number of white blood cells varied from 9000 to 36,000. In this series we were able to verify the fact that a marked increase of nonsegmented polymorphonuclear cells may occur in conditions other than infections. This tends to emphasize the importance of recognizing degenerative changes in the cytoplasm of the polymorphonuclear leukocytes.

3. *Infections—Recovered Cases.* Interesting blood reactions were observed in this study of cases which included various infections, such as mastoiditis, appendicitis, lobar pneumonia, empyema, puerperal sepsis, etc. Certain localized infections, such as mastoiditis, appendicitis, subperiosteal abscess and similar conditions, may not be associated with either leukocytosis, polynucleosis or toxic changes unless there is an extension of the process or complications occur: then there is first an increase of the segmented polymorphonuclear cells followed by a rapid increase of the nonsegmented forms. In more severe infections, such as pneumonia or transient bacteriemia, our results correspond with the findings of Mommsen,[13] in that there is a marked increase of the polymorphonuclear cells with degenerative granules early in the infection and a complete disappearance of these cells with recovery. The degenerated index is at first rather high (21 to 93 per cent) in the first examination of patients on admission to the hospital. In all these cases there was a gradual diminution in the numbers of the degenerated cells, with complete disappearance on recovery.

TABLE 2.—ILLUSTRATIVE CASES.

Case No.	Diagnosis.	Blood culture.	Leukocytes.	Nonsegmented polymorphonuclears, per cent.	Segmented polymorphonuclears, per cent.	Lymphocytes, per cent.	Monocytes, per cent.	Degenerative index.	Remarks.
1	Menorrhagia	Not done	6,400	6	54	34	6	0	Recovered
2	Splenectomy (purpura)	Not done	36,000	34	63	2	1	0	Recovered
3	Ectopic gestation	Not done	29,800	14	81	3	2	2	Recovered
4	Mastoiditis	Negative	6,200	7	46	44	3	0	Recovered
5	Appendicitis with abscess	Not done	12,200	4	79	12	5	0	Recovered
6	Pneumonia	Negative	10,000	47	42	6	5	86	Recovered
7	Empyema	Not done	26,000	29	41	19	8	100	Recovered *
8	Typhoid fever	Bacillus typhous	4,000	49	32	12	4	28	Recovered
9	Puerperal sepsis	Streptococcus (in flasks)	9,400	41	31	27	1	76	Recovered
10	Ulcerative colitis	Negative	17,400	37	17	37	9	85	Recovered *
11	Subacute bacterial endocarditis	Streptococcus viridans	17,000	49	38	8	5	10	Died
12	Subacute bacterial endocarditis	Streptococcus viridans	8,400	52	40	6	1	100	Died
13	Miliary tuberculosis	Not done	6,600	35	53	9	3	97	Died
14	Pneumonia	Pneumococcus (Type I)	11,000	68	25	6	1	95	Died
15	Pneumonia	Pneumococcus (Type II)	10,000	57	37	4	2	100	Died
16	Sepsis	Staphylococcus aureus	14,000	42	37	15	6	92	Died
17	Suppurative pyelonephritis	Bacillus coli	7,000	64	13	9	6	100	Died
18	Meningococcus sepsis	Meningococcus	27,400	52	33	6	6	20	Died
19	Diphtheritic laryngitis	Not done	60,000	61	30	4	5	100	Died
20	Malignant leukopenia	Negative	1,800	41	10	44	5	88	Died
21	Ulcerative carcinoma of uterus	Not done	4,400	34	62	2	2	95	Died

* Transfusion.

In cases of widespread infection, especially in pneumonia, the degenerative index was found to fall gradually after the crisis. In these instances the curve more nearly approximated the underlying disease than the clinical picture, temperature, pulse, etc. This was also true in a case of postabortive sepsis in which the temperature rapidly returned to normal after the spontaneous expulsion of placenta. The persistence of degenerated cells after the temperature, pulse and total white blood count have returned to normal strongly suggests that, even despite apparent clinical recovery, the underlying process is not entirely healed.

It is important to note that a high degenerative index is not necessarily accompanied by a fatal outcome. On following these cases repeatedly it was found that a persistence of a high degenerative index is usually a warning of the persistence of severe infection or deep suppuration which may require surgical intervention. An example of this is a case recently observed in one of the surgical wards, of a middle-aged man who complained of pain, of 6 days duration, in the right lower quadrant of the abdomen. After admission to the hospital the pain subsided somewhat, and palpation of the abdomen did not show rigidity or tenderness. His temperature and pulse were normal; the blood picture was approximately normal as the number of white blood cells and polymorphonuclear cells were concerned. According to the hemogram, the blood picture was as follows:

White blood cells, 9300

	Per cent.	
Nonsegmented polymorphonuclear neutrophils	15	
Segmented polymorphonuclear neutrophils	52	
	—	67
Lymphocytes	28	
Monocytes	5	
Degenerated polymorphonuclear cells	2	

Degenerative index (2 ÷ 67), 3

The patient's condition improved clinically, so that surgical interference seemed unwarranted. The degenerative index, followed from day to day, ran contrary to the clinical course and, based on our past experience, the findings seemed to indicate the presence of suppuration. On the third day of admission the blood picture showed a degenerative index of 56 and showed the following:

White blood cells, 13,400

	Per cent.	
Nonsegmented polymorphonuclear neutrophils	24	
Segmented polymorphonuclear neutrophils	42	
	—	66
Lymphocytes	29	
Monocytes	5	
Degenerated polymorphonuclear cells	37	

Degenerated index (37 ÷ 66), 56

On the fifth day tenderness reappeared in the right lower quadrant and an indefinite mass was distinctly felt. At this time the degen-

erative index again rose to 68. His temperature at no time was higher than 100° F. and the pulse remained normal. An abdominal exploration was made and a large retrocecal abscess was found. The day following the operation the degenerative index reached 89, and then gradually fell so that 15 days after operation, when the patient had fully recovered, only 2 per cent of the cells were found to be degenerated.

These findings should suggest the importance of additional data concerning the character of the cytoplasmic changes in the leukocytes in surgical cases and may explain some of the apparent discrepancies between blood picture and operative findings.

4. *Suppurative Conditions—Fatal Cases.* The degenerative index in all of these cases was usually high, or rapidly rose to a high percentage. The trend of the index was upward, in contrast to the trend in the recovered cases. There appeared to be more correspondence with the clinical symptoms and final course of the disease than with the number of the staff polymorphonuclears. The lowest degenerative indices were found in Streptococcus viridans and in meningococcus infections; it was somewhat higher in Streptococcus hemolyticus infections, and was highest in pneumococcus and staphylococcus infections. (Table 2.)

Many degenerative cells were found in the blood smear in a case of carcinoma. The degenerative index was high (95). At postmortem examination an ulcerative, sloughing, infected carcinoma of the uterus was found.

The persistence of a degenerative index between 90 and 100 is of grave prognostic import and is usually followed by death.

Illustrative Cases. Two typical cases are described to show the correlation between the course of the disease and the degenerative index.

Case Reports.—CASE 1. A negro, aged 27 years, was admitted to the hospital, with a history of cough (3 days), weakness, and chilliness (1 day). The temperature was 105.4° F., and signs of pneumonia of the left lower lobe were found. On the seventh day of the disease the temperature came down by crisis. The number of white blood cells varied from 29,000 to 36,000 during the first 2 days and later was 20,000. The white blood count remained elevated long after the fever had subsided, with a sharp, fleeting rise of 1 day's duration 3 days after the crisis. (Table 2). The nonsegmented polymorphonuclear cells ranged from 61 per cent on the day of admission to 27 per cent the day of discharge. Myelocytes and myeloblasts were 8 per cent on admission and they gradually diminished, so that none were present in the blood smear the day of discharge. The degenerative index on admission was 93 and remained around 80 until the day after the critical fall of the temperature. At this time the degenerative index fell to 40. On the fourth day after the crisis, the degenerative index again rose to 97 and remained at that level for 3 days, dropping afterward toward normal.

A secondary rise in pneumonia shortly after the crisis has previously been noted by Mommsen.

TABLE 3.—S. A. PNEUMONIA.

Date, 1930.	White blood cells.	Polymorphonuclears.		Lymphocytes.	Monocytes.	Degenerative index.
		Nonsegmented.	Segmented.			
Nov. 18 . .	29,000	61	29	3	7	93
Nov. 19 . .	36,000	47	42	10	1	84
Nov. 21 . .	20,000	44	50	4	2	83
Nov. 24 . .	18,000	42	50	6	2	80
Nov. 25 . .	22,000	54	39	3	4	40
Nov. 27 . .	33,600	45	39	10	6	97
Nov. 28 . .	23,800	41	47	8	4	98
Nov. 29 . .	22,000	44	42	6	8	96
Dec. 1 . .	16,000	26	48	14	12	79
Dec. 3 . .	13,000	27	56	12	5	38*

* Discharged. The blood count on the day of discharge, showing a moderate leukocytosis, a high percentage of nonsegmented cells, as well as a degenerative index of 38, suggests that we are at times discharging patients from the hospital before the disease process is entirely healed, and indicates the necessity for an extension of the convalescent period.

In the other cases of our series we were impressed with the fact that the curve of the degenerative index may at times follow more closely the underlying pathologic process than the temperature or the ordinary white blood count. This seems most likely to occur in pneumonia. A Roentgen ray examination of the chest 3 days after the crisis showed that the left lower lobe was undergoing resolution.

CASE 2.—A woman, aged 56 years, entered the hospital complaining of fever for 8 days.

Past history: Mastectomy 12 years ago, pneumonia 3 years ago, and painful finger joints for many years. Four months ago the patient had an infected finger followed by extensive swelling, redness and tenderness of the arm, with chills, fever (106° F.), and weakness. The chills and fever subsided after 10 days, but the weakness continued. Three months ago she was seized with a severe paroxysm of pain in the back, accompanied by high fever 101° to 105° F.), profuse sweats, loss of appetite, and delirium.

Upon admission, the patient was found to be breathing rapidly; there were râles at both bases, and edema of the legs; she appeared acutely ill. The temperature mounted steadily and marked weakness and sweats continued. A week after admission there was severe pain in the legs followed by the appearance of phlebitis in the right calf. A blood culture taken on the ninth day after admission showed Streptococcus hemolyticus; 11 days after admission she became stuporous and died. The postmortem examination showed suppurative spondylitis and perispondylitis of the fifth lumbar and fifth sacral vertebræ, right pyosalpinx, and right femoral phlebitis.

The study of the leukocytes in this case showed that the total white blood cells remained the same throughout the course of the disease. The degenerative index on admission was 80 and rose gradually, persisting around 88 for 5 days. On the thirteenth day in the hospital all the polymorphonuclear neutrophils showed

degenerative changes; the degenerative index was 100. (Table 3.) The hemogram in the fatal cases showed, in most instances, a high degenerative index. In the cases which were followed serially the degenerative index remained high, rising toward 100 as the disease progressed to a fatal issue. It was not unusual to see a fatal result in cases with a degenerative index of 100.

TABLE 4.—C. G. STREPTOCOCCUS HEMOLYTICUS SEPSIS.

Date, 1930.	White blood cells.	Polymorphonuclears.		Lymphocytes.	Monocytes.	Degenerative index.
		Nonsegmented.	Segmented.			
Sept. 11 . .	19,600	38	48	11	3	80
Sept. 16 . .	18,600	55	32	10	3	88
Sept. 17 . .	16,600	57	39	3	1	83
Sept. 18 . .	20,600	53	42	3	2	88
Sept. 20 . .	16,650	72	20	5	3	87
Sept. 22 . .	21,000	54	44	2	0	100*

* Exitus.

Summary. A study of the blood in various types of infection shows marked variation in the number of leukocytes and in the number of nonsegmented and segmented polymorphonuclear cells. Reports of ordinary blood examination limited to the number of leukocytes and the percentage of polymorphonuclear neutrophilic cells may be misleading and are not helpful in formulating conclusions, either of a diagnostic or a prognostic character.

The division of the polymorphonuclears into nonsegmented and segmented polymorphonuclear neutrophils is important. The first response in infection apparently is an increase in the number of leukocytes and of the segmented cells. Then the nonsegmented cells increase rapidly. The increase of these immature cells indicates a growing activity of the bone marrow and not necessarily an infection.

Cytoplasmic granular changes in the polymorphonuclear leukocytes appear in certain infections. The changes include marked basophilia of the granules and, less frequently, vacuolization of the cytoplasm and certain cytoplasmic masses known as Doehle bodies. The basophilic, or "toxic," granules are seen only in infections—most often in bacteriemias. In streptococcus infections they occur late, particularly in subacute endocarditis; but in other conditions, especially those associated with more or less extensive suppuration (as in pneumonia) they make their appearance early and usually persist for weeks after the crisis. The cells showing "toxic" granules occur in both the segmented and nonsegmented polymorphonuclear neutrophils. The absence of "toxic" granules is suggestive of a mild or localized infection. A persistence of this condition indicates a good prognosis or the absence of complications.

The absence of "toxic" granules or degenerative changes in the cytoplasm of the polymorphonuclear leukocytes in cases of severe infection is unusual.

The degenerative index offer a prognostic guide in infectious conditions. A decrease of the degenerative index is an indication of recovery. A steady increase of the degenerative index is sugtive of either a complication or a bad prognosis. A degenerative index over 90 per cent is usually associated with a severe infection, regardless of the clinical condition of the patient and is of unfavorable significance.

Frequent observations of patients through the study of nuclear changes, such as segmentation and nonsegmentation, combined with a consideration of the cytoplasmic changes, are a most valuable aid in gauging the severity and course of infections.

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TRICHINIASIS. A DISCUSSION, WITH REFERENCE TO ELEVEN RECOVERED CASES IN A FAMILY.

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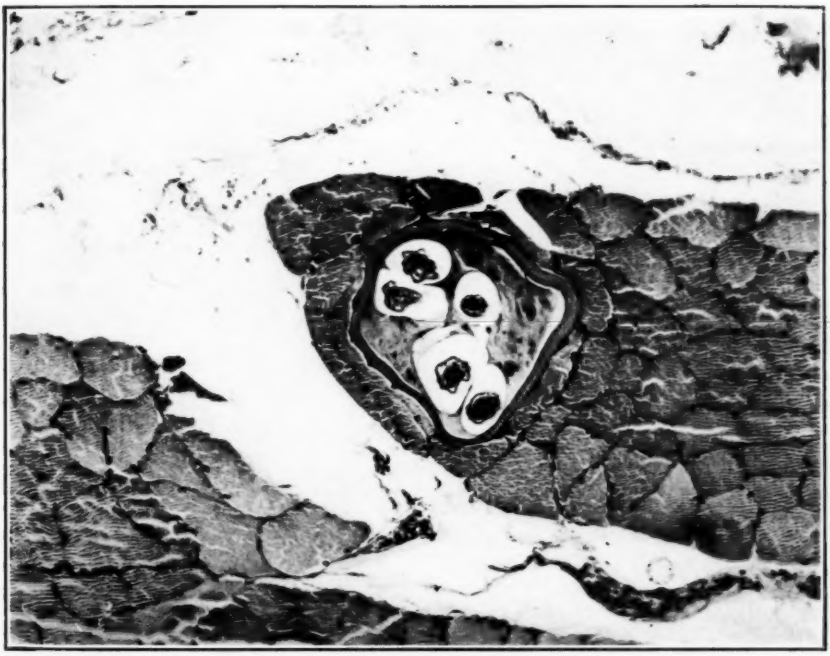
Trichina infection, not a rarity in recent years with the rigid governmental regulations of commercial meat products, is always of sufficient interest to claim the physician's attention. This is true because of the fact that the disease is preventable, it presents a variable and interesting clinical picture, it is now one of the reportable diseases, there is no specific treatment once the larvæ have invaded the voluntary muscles and, if a sufficiently large number of the parasites are ingested, the outcome may be fatal.

Historical. In the latter half of the 19th century there arose no little controversy as to the names of those investigators who should receive credit for the discovery of the parasite causing trichiniasis. The literature of that period abounds with bitter comments, particularly between the English and German writers, and shortly afterward the discussion was continued in this country. When one recalls that the public health aspect of trichiniasis was responsible for considerable international friction[1] it is not surprising that prejudices of personal opinion in this regard might have been entertained.

Any dispassionate survey of the literature can hardly afford to omit the name of Tiedemann[2] who, in 1821, observed small, calcified bodies in the muscular system of a man who had died of "thoracic dropsy." He described these bodies as being "from two to four lines long and round" and submitted the result of their chemical nature, the latter indicating that, in addition to their calcareous constituents, they contained organic matter resembling "albumen or fibrin."

This remarkable observer has been partially discredited only because of his statement as to the size of the calcified bodies, obviously much larger than is actually the case. It seems likely, however, that his was the first published record of the encysted trichina larvæ.

In 1828 Peacock[3] noted the calcified specks in a case at autopsy,



Photomicrograph of a section of muscle removed from the father's leg 6 months after infestation.

prepared a specimen from the sternohyoid muscle and placed it in the museum of Guy's hospital. Five years later Hilton,[4] another Englishman, discovered what was unquestionably the encysted larvæ and suggested their parasitic nature. In 1835 Prof. Richard Owen[5] described a parasite of man, under the name of trichina spiralis, certain small worms which had been found by Paget, then a medical student, in a cadaver in London. Owen generously stated that Wormwald, a demonstrator in the anatomy laboratory, had previously pointed out to him that on numerous occasions sandlike particles in the muscle systems of postmortem specimens had dulled his dissecting knives. Joseph Leidy,[5a] one of the greatest American biologists of the 19th century, was the first to find trichina spiralis in hogs (1846). Herbst (1851–1852),[6] an experimental physiologist in Göttingen, appears to have been the first to have experimented with the life history of the parasite. In 1860 Professor Zenker[7] of Dresden showed it to be the cause of a disease that has since been named trichinosis, and which prior to his observations had been confounded with typhoid fever and other maladies. The brilliant observations and experiments of Zenker,[7] Leuckart,[8] Virchow,[9] and others thus placed the medical profession in possession of detailed data concerning the life history of, and source of infection by, the parasite under discussion; also the symptoms, duration and other clinical details of the disease and the preventive measures to be adopted.

In 1896 Brown[10] pointed out the eosinophilia that has since been regarded so characteristic of the disease. Opie,[11] experimenting with guinea pigs fed with trichinous meat, noted the variations in the eosinophilic cells in mild and severe infections. Frothingham[12] described the intestinal lesions in rats, and later[13] noted that in the human the larvæ enter by the lymph stream and are distributed by the circulating blood. In 1909 Herrick[14] and Janeway recovered the larvæ from the circulating blood; 5 years later van Cott and Lintz[15] first observed their presence in the cerebrospinal fluid *in vivo*.

Recently we have been permitted to study 11 cases of trichinasis in a family. A summary of the history is as follows:

Case Reports. On April 30, 1930, an Italian father at Clyde, N. Y., purchased smoked ham from a local grocer. (The product was obtained from a well-known commercial meat packing company.) That evening the father, mother and their 9 children ate sandwiches made from the uncooked ham. Four days later the entire family became ill with nausea and diarrhea. (The remainder of the above-mentioned ham was sold to other patrons for frying purposes and no illness resulted therefrom.) These symptoms, together with lassitude, persisted for 6 days, when one of us (G. S. A.) was called to attend the mother. She presented nausea, marked prostration, a rapid pulse and a temperature of 103° F. The following day she was improved and the family physician was asked to discontinue his visits. On May 21, 1930, 18 days after the onset of the illness, the

father consulted his physician because of weakness and anorexia. Marked edema of the eyelids was noted and a differential blood count revealed 23 per cent eosinophils. That afternoon we examined the family, all members of which showed some evidence of the disease. The prominent symptoms of which all complained were: Nausea, diarrhea, pain in the legs, shoulders and back. The entire group had, or had had, edema of the eyelids and of the face over the malar regions. The following résumé is a summary of the interesting features of each case, including the observations made 6 months later.

FATHER, aged 45 years. Complaint: Severe pain in the shoulders, weakness and anorexia. Examination: Prostration, sweating, edema of eyelids, marked tenderness of shoulder and leg muscles. Temperature, 99.2° F. Eosinophils, 23 per cent. Progress: May 23: Palpable spleen. May 25: Developed hoarseness and cough; bronchopneumonia followed; Weakness persisted until latter part of June. November 21: Feels well; palpable spleen; slight tenderness of right leg; eosinophils, 4 per cent.

MOTHER, aged 33 years. Complaint: Weakness and exhaustion. Examination: Tenderness over suprascapular regions and in leg muscles. Temperature, 99.6° F. Eosinophils, 33 per cent. Progress: Diarrhea continued until July 1. Muscular pains and epigastric pains after eating were moderately severe during the first week in June. November 21: Slight tenderness of legs; palpable spleen; eosinophils, 7 per cent.

MARIE, aged 11 years. Complaint: None. Examination: Slight edema of eyelids; tender, tense, swollen leg muscles. Temperature, 103° F. Eosinophils, 10 per cent. Progress: May 24: Developed cough; no râles heard. May 28 to June 15: Upper abdominal pain after eating. November 21: No symptoms or signs. Eosinophils, 1 per cent.

IRENE, aged 10 years. Complaint: Pain in the legs. Examination: Slight edema of the eyelids; tenderness over suprascapular regions; legs are tense and slightly tender. Temperature, 100° F. Eosinophils, 13 per cent. Progress: May 27 to June 25: Occasional epigastric pain after eating. November 21: Feels well; palpable spleen; eosinophils, 8 per cent.

FRED, aged 5 years. Complaint: "Legs feel cold." Examination: Marked edema of eyelids; tenderness in legs, forearms and arms. Temperature, 100.6° F. Eosinophils, 14 per cent. Progress: May 23: Hoarseness. May 24: Palpable spleen. May 25: Upper abdominal pain, usually after eating. June 15: Indefinite abdominal pain after eating. November 21: Feels well; palpable spleen; eosinophils, 13 per cent.

JAMES, aged 9 years. Complaint: Pain in the shoulders. Examination: Slight edema of eyelids; tenderness over suprascapular regions. Temperature, 100.8° F. Eosinophils, 28 per cent. Progress: May 24: Epigastric pain after eating. May 25: Severe epigastric pain after eating. June 14: Abdominal cramps in the morning. November 21: Pain and tenderness in legs; palpable spleen; eosinophils, 5 per cent.

SAM, aged 13 years. Complaint: Weakness and lameness of legs. Examination: Pallor, edema of left eyelids; hoarse cough; palpable, nontender spleen. Temperature, 102.2° F. Eosinophils, 28 per cent. Progress: May 27: Palpable spleen; irregular pulse. May 28: Dry cough. May 29: Edema of right side of face. May 31: Pallor. June 2 to 4: Abdominal pain after eating. June 15: Occasional abdominal cramps after eating. November 21: No complaints; palpable spleen; eosinophils, 3 per cent.

AGNES, aged 7 years. Complaint: None. Examination: Marked edema of eyelids; tenderness of left leg. Temperature, 99.2° F. Eosinophils, 21 per cent. Progress: May 21: Nightsweats. May 27 and 28: Epigastric pain after eating. June 4: Diffuse abdominal pain. June 15:

Occasional epigastric pain after eating. November 21: Feels well; edema of face and eyelids; palpable spleen; eosinophils, 9 per cent.

GEORGE, aged 15 years. Complaint: Weakness. Examination: Tenderness in legs. Temperature, 98.6° F. Would not permit drop of blood to be taken. Progress: Mild course. Would not allow further examinations.

MARGARET, aged 14 years. Complaint: Pain in left leg. Examination: Tenderness of left leg; edema of eyelids. Temperature, 99.2° F. Eosinophils, 38 per cent. Progress: May 24: Nightsweats; palpable spleen. May 25 to 27: Feels well. May 28 to June 2: Epigastric pain soon after eating. November 21: No symptoms or signs; eosinophils, 2 per cent.

ANN, aged 2 years. Complaint: None. Examination: Slight edema of eyelids. Temperature, 98.6° F. Eosinophils, 38 per cent. Progress: Mild course; had sweats, pain in legs and edema of lids. November 21: No symptoms or signs; eosinophils, 5 per cent.

TABLE 1.—DIFFERENTIAL COUNT 18 DAYS AFTER INFESTATION.

Patient.	Age, yrs.	Polymorphonuclears, per cent.	Large and small lymphocytes, per cent.	Transitionals and large monocytes, per cent.	Eosinophils, per cent.	Basophils, per cent.
Father	45	64.0	11.0	2	23.0	1.0
Mother	33	42.0	18.0	7	33.0	0
Marie	11	60.0	25.0	5	10.0	0
Irene	10	51.0	31.0	5	13.0	0
Fred	5	56.0	27.0	3	14.0	0
James	9	50.0	20.0	2	28.0	0
Sam	13	55.0	15.0	2	28.0	0
Agnes	7	63.0	13.0	2	21.0	0
Margaret	14	38.0	21.0	1	38.0	2.0
Ann	2	34.0	28.0	1	37.0	0
Average	..	51.3	20.9	3	24.5	0.3

TABLE 2.—DIFFERENTIAL COUNT 6 MONTHS LATER.

Patient.	Age, yrs.	Polymorphonuclears, per cent.	Large and small lymphocytes, per cent.	Transitionals and large monocytes, per cent.	Eosinophils, per cent.	Basophils, per cent.
Father	45	58.0	35.0	3.0	4.0	0
Mother	33	60.0	31.0	1.0	7.0	1.0
Marie	11	55.0	41.0	3.0	1.0	0
Irene	10	45.0	42.0	4.0	8.0	1.0
Fred	5	35.0	47.0	4.0	13.0	1.0
James	9	64.0	30.0	1.0	5.0	0
Sam	13	45.0	47.0	3.0	3.0	2.0
Agnes	7	43.0	46.0	2.0	9.0	0
Margaret	14	59.0	36.0	3.0	2.0	0
Ann	2	40.0	53.0	2.0	5.0	0
Average	..	50.4	40.8	2.6	5.7	0.5

At various times during our observations we attempted to gain permission to excise a portion of muscle for microscopic diagnosis

but were unable to do so until 6 months after the onset of the illness. Illustration* is a photomicrograph showing the encysted trichinæ in a section of muscle removed from the father's leg.

Table 1 is a summary of the differential blood counts made on May 21, 1930, 18 days after the family became ill. In Table 2 are recorded the differential counts made on November 21, 1930, 6 months later.

Discussion. Certain features of these cases seem of sufficient interest and importance to warrant further consideration.

1. *Eosinophilia.* Eosinophilia has been considered of diagnostic importance since Brown's[10] first observations in 1896, and since whose contributions the presence of an eosinophilia has come to be regarded by many as essential in the diagnosis. However, although characteristically true, it is not an invariable finding, as a review of the literature clearly shows that many serious cases of trichina infection have occurred in which no eosinophilia was present. We have therefore regarded it of interest to review the more important observations that have been made on this subject.

T. R. Brown's[10] original case showed 68.2 per cent eosinophils. Barker[16] and Thayer,[17] commenting on this case, declared this unusual blood picture to be unique in medical literature. One year later Thayer[18] cautiously expressed the opinion that until further studies had been made, it could hardly be said that trichiniasis was the only type of myositis that might have an associated eosinophilia. In 1898 Brown[19] published his important monograph and concluded that "there is a marked increase in the percentage of eosinophilic cells in the blood . . . this increase may be used as a diagnostic sign in the disease." Thompson[20] later believed that "a high degree of eosinophilia is invariably present; usually 30 per cent and frequently much higher, even above 80 per cent." Leen[21] thought that the eosinophilia stood in close relation to the migration of the embryos and their entrance into the musculature, and that for months or even years after recovery these cells were increased. Cabot[22] mentioned a case in which there was no increase in the eosinophils until 10 days after the onset of the disease. It will be recalled that all of our cases showed a distinct eosinophilia during the third week. (Table 1.)

Opie,[11] working with guinea pigs fed with trichinous meat, was led to believe that there was no constant alteration of the number of eosinophils until the end of the second week after infection, when the relative and absolute number rapidly increased and reached a maximum at the end of the third week. He was of the opinion that the number of eosinophilic leukocytes in the blood always diminishes before death, so that the proportion was usually less than 1 per cent. He further concluded that infections with a very large number of parasites caused a rapid diminution of the eosin-

* Specimen prepared by Department of Pathology, Syracuse University College of Medicine.

ophils and was quickly fatal, whereas mild infections stimulated these cells to active multiplication.

Gregg[23] reported the case of a boy who had only 10 per cent eosinophils after 3 weeks of the disease and believed at that time there was no parallel case in the literature. DaCosta[24] later cited a patient without fever or history of infection in which trinchinæ were found in an inflamed leg muscle and in which no eosinophilia was present. Bartlett's[25] case showed only 1 per cent eosinophils before death. Howard[26] reported a fatal case without eosinophilia but with a large number of eosinophils in the muscle lesions. McDonald and Waddell[27] reported 43 cases in which 12 per cent did not show an eosinophilia. Other observers[15, 20, 28] were of the opinion that the degree of eosinophilia afforded no accurate index of the severity of the disease. The observations in our non-fatal cases would tend to support this latter opinion. Weiss[28] commented that "the prognosis is poor when there is a sudden drop in the eosinophil count." Jaisohn[29] concluded from a study of an epidemic that the sudden subsidence of leukocytes and reduction of eosinophils indicated an unfavorable termination. Recently Aldridge[30] has reported a series of 29 cases, all of whom had a definite eosinophilia except the 2 patients who died.

It therefore becomes apparent that an eosinophilia is not a constant or invariably dependable finding in trichina infections. As has already been pointed out, it may be absent during the entire course of the disease; again, the increase in the relative numbers may not be present until 1 to 3 weeks after infection. It has never been established that the degree of eosinophilia bears any relationship to the severity of the disease except, possibly, in the fatal cases. A review of the literature suggests that those cases failing to exhibit an eosinophilia at all times during the acute stages of the disease are to be regarded as the ones most unlikely to recover. The suggestion is offered that a more general appreciation of the above observations might prevent serious errors in diagnosis and prognosis.

2. *Palpable Spleen.* One of the most interesting features noted in our cases was the splenic enlargement. Some years ago, when trichiniasis was more frequently confounded with typhoid, the absence of a palpable spleen was thought to be a point of differentiation in favor of the former. Neither Osler[31] nor Cecil[32] mentions the presence or absence of a palpable spleen in a discussion of trichiniasis. It is of some interest that 1 of the 3 cases Brown[19] described in 1898 had a palpable spleen, although no further comment was made concerning its presence.

Frothingham[13] described a case that came to autopsy in which there was no splenomegaly. Leen[21] declared the spleen not to be enlarged in trichiniasis, but that if it were found to be palpable, it was due to a mixed infection and not a peculiarity of the disease. van Cott[15] noted no enlargement in 10 cases.

At the time of our first examination, during the third week of the illness, in only 1 case was a palpable spleen discovered, (Sam, aged 13). Two days later one of us (G. S. A.) found a palpable spleen in the father. The following day the spleen was palpable in 2 more of the cases (Fred, aged 5 and Margaret, aged 14). All of the cases were observed daily until June 15 without further evidence of splenic enlargement in the remaining cases.

Because of their apparent recovery they were not seen again until 5 months later (November 21, 1930), at which time we examined the 10 available cases and found that 7 of them had a palpable spleen. Except in 1 case (Margaret, aged 14), all of the cases who developed a palpable spleen during the active stage of the disease also presented this finding 6 months later. Eight of the cases, then, had a palpable spleen at one time or another during the period of our observations, and 4 cases had a palpable spleen during the third week, at a time when the symptoms of their illness were most acute. We were unable to make a final examination of 1 patient (George, aged 15) because of his incorrigible attitude.

The presence of a palpable spleen is of considerable interest, and its significance is indeed difficult to evaluate. It is hoped that these observations may be borne in mind by others who may see cases of trichiniasis. Possibly careful studies on those cases coming to necropsy may offer a definite explanation of the phenomenon.

3. *Diagnosis and Symptomatology.* The usual picture of trichiniasis offers little difficulty in diagnosis. Most frequently cases are seen in groups and a common source of infection is ascertained. The characteristic symptoms of gastrointestinal irritation, the fever, the muscular pains, the edema of the eyelids and the eosinophilia are noted in the majority of nonfatal cases when sufficient trichinous meat has been eaten.

It is certainly true that isolated, unrecognized and atypical cases of trichiniasis do occur and occasionally there is no history of infection in proven cases of the disease. We recall the instance of one family in which the mother became infected although the father and four children escaped. All had eaten of the same piece of insufficiently cooked, home-cured pork. As early as 1901 Williams[33] reported finding trichinæ in 5.3 per cent of 505 unselected autopsies. All of the subjects had died of other disease than trichiniasis, hence "the infection with trichinæ must, in every case, have occurred a considerable time previously." Conner[34] has recently drawn attention to the atypical forms of trichiniasis. "Trichiniasis presents a clinical picture of much greater variability than is the case of most specific diseases," he says, and concludes that there are cases that run an afebrile course and that in some patients the characteristic eosinophilia may be lacking; that some cases may resemble acute nephritis, acute meningitis or sinusitis; that other patients may exhibit conspicuous and alarming throat symptoms and others may have epigastric pain as the chief or only symptom of the disease.

MacKenty[35] has focused attention on the cases with predominating laryngeal symptoms. Such patients, he says, may have cough, pain on swallowing and on phonation, and a harsh voice. A point of some interest is that the edema of the throat and larynx in his cases appeared more like passive edema rather than that due to an acute surface inflammation. Thomas[36] and Pratt[37] have described rather atypical cases of trichiniasis in which the predominant symptoms are referable to the sinuses.

The gastrointestinal and abdominal symptoms are subject to considerable variation and are of great interest to the physician who attempts to evaluate their probable causes. It is likely that the early symptoms of nausea, diarrhea and vomiting are due to mechanical irritation of the intestine at a time when the parasites are penetrating the mucous membrane. Frothingham[12] has demonstrated the manner of this invasion and pointed out that some of the epithelium, where stripped off, becomes necrotic. In spite of this fact, diarrhea is by no means a constant symptom. Thompson[20] suggested that it occasionally occurs as an immediate symptom when it appeared due to botulismus rather than to irritation by the trichinæ. All of the cases reported in our series had diarrhea during the first week of the disease, but only 1 case, the mother, had the symptom after the second week. In her case the diarrhea persisted for more than 2 months.

The variety of the types of abdominal pain in any group of cases is fascinating. Possibly the early cramplike abdominal pains, during the period of invasion, are due to localized intestinal spasm. When one reflects that the larvæ have been found in the mesenteric lymph nodes[38] and for a time are abundant in the peritoneal cavity;[39] that the embryos may break out of the vessels in the liver and pancreas[13] and cause local destruction of tissue; and finally that death usually occurs as the result of penetration of the intestinal wall,[39] it is not difficult to agree that no typical abdominal distress could be anticipated in any case or group of cases. It was of interest that the majority of our cases complained of abdominal pain, chiefly epigastric and usually after eating, about 3 weeks after their infection. No spasm or rigidity of the abdominal muscles was noted. One patient (James, aged 9) had the mild epigastric pain at the same time as the other cases, but 2 weeks later began to have severe abdominal colic each morning between 8 and 9 o'clock. The pain was severe, the temperature normal, the distress had no relation to the ingestion of food. The paroxysms lasted from ½ hour to 1 hour, the boy cried and rolled about on the bed and always vomited whatever was given by mouth to ease the discomfort. No localized tenderness or spasm could be elicited and after the paroxysm he remained free from pain for the remainder of the day.

It has long been recognized that many cases of trichiniasis may have respiratory symptoms. To Opie[11] and Frothingham[13] we owe our conception of the pathologic processes taking place in the lungs.

One of our cases had a definite bronchopneumonia. Five cases developed a cough without rise in temperature and 3 cases presented rather marked hoarseness. The laryngeal pathology in these cases has been referred to elsewhere.[35] MacCallum[39] has called attention to the bronchitis in some of the fatal cases.

4. *Laboratory Aids in Diagnosis.* The variations in the presence, degree, or absence of eosinophilia has already been discussed. Following Staübli's[40,41] work, Herrick and Janeway[14] demonstrated the presence of trichina embryos in the circulating blood. Their method was to lake the blood with 10 to 15 parts of 3 per cent acetic acid, centrifuge and examine the sediment microscopically. Obviously this method is of value only during the period of migration.

Formerly the presence of a positive Widal test was thought to differentiate definitely between typhoid and trichiniasis. This cannot be said to be invariably true, since Maase and Zondek[42] have reported 3 cases of trichiniasis with positive Widals, and Conner[34] has drawn attention to the fact that rarely the differentiation from typhoid may be rendered difficult by the presence of a strongly positive Widal reaction. It is of interest that 1 of Brown's[19] 3 cases had a positive Widal, but it was said this patient had had typhoid fever 6 months previously.

Since Van Cott and Lintz[15] first reported the finding of embryo trichinæ in the spinal fluid *in vivo*, many other workers[27,43,44,45,46,47,48] have confirmed the observations. Apparently trichiniasis may present the clinical picture of acute meningitis and Meyer[44] has pointed out that in cases in which the embryos have been found in the spinal fluid the cell counts varied between 40 to 240 lymphocytes per c.mm. His warning in this regard was that in such instances it might be difficult to differentiate between poliomyelitis, were it not for the presence of the embryos in the cerebrospinal fluid.

There is considerable variation of opinion as to the presence of the parasites or embryos in the stools of patients suffering with trichiniasis. Most observers[15,20,27] agree that the parasites or ova are not to be found in the stools. As early as 1864 Fiedler[49] made the suggestion that the adult parasites were dissolved in the small intestine and therefore were not to be discovered in the stools. Van Cott and Lintz[15] have expressed a similar view. Other writers[15,50,51] were of the opinion that the embryos were not to be found in the stools since they were not discharged into the lumen of the intestine. Stitt[52] states: "During the diarrheal stage we may examine the stools for adult worms, in particular dead males or possibly actively motile embryos." Osler[31] declares: "The worms may be found in the stools or in the duodenal contents." Weiss[53] has recently reported the finding of both the adult parasites and ova in the stools. Only 1 of our cases had a diarrhea at the time we saw the patients but we were unable to demonstrate the presence of adult parasites or their embryos in her stool specimens. The review of the literature suggests that the detection of the parasites or the

embryos is of infrequent occurrence and that therefore the examination of the stools offers little diagnostic data as compared to other, more regularly dependable laboratory procedures.

Summary. 1. Eleven recovered cases of trichiniasis in a family are reported.

2. Marked eosinophilia was present in each case.

3. A review of the literature, with reference to the diagnostic importance of eosinophilia, is presented. Attention is directed to the fact that eosinophilia is not a constant and infallible diagnostic criterion.

4. A palpable spleen was noted in 4 of the 11 cases during the first 3 weeks of the disease; 6 months later 7 of 10 cases had a palpable spleen.

5. A brief discussion of the symptomatology, clinical manifestations and the diagnostic criteria of trichinosis is presented.

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PRIMARY ANGIOFIBROMA OF THE DIAPHRAGM.

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As Lucké[1] has shown, primary tumors of the diaphragm are rare, less than a score having been reported. All of these have been of connective tissue origin, namely, fibromas, chondromas, lipomas and sarcomas. The purpose of this paper is to report an additional case, that of an angiofibroma.

Case Report.—J. S., a white male, aged 50 years, was admitted to the Tuberculosis Service of the Philadelphia General Hospital, November 12, 1931. His history and clinical course were typically those of extensive pulmonary tuberculosis. Physical examination showed extensive involvement of both lungs and the sputum was positive for tubercle bacilli. No other findings of significance were noted.

Roentgenologic reports were as follows: Both lobes of the left lung show considerable irregular density; two radiolucent areas are present in the left upper lobe; the left diaphragm is not visualized; the upper portion of the right upper lobe, especially in the infraclavicular region, shows marked irregular density, the remainder of the lobe being mottled to a lesser degree; the right apex also shows a radiolucent shadow; the heart is displaced to the left; in the anteroposterior view the mesial half of the right diaphragm is the seat of a large, well-defined shadow, the upper border of which is convex; the base measures 8 cm. (Fig. 1). On profile view, this shadow is somewhat rectilinear in shape, measuring approximately 11 by 4 cm.; it extends from the xiphoid dorsalward to a point just posterior to the mid-axillary line (Fig. 2). Fluoroscopic examination shows this tumor mass to move synchronously with the diaphragm. Roentgen diagnosis: Extensive ulcerative fibrocaseous tuberculosis of left lung and upper lobe of right lung, with cavitation of both upper lobes; atelectasis of left lower lobe; neoplasm arising either from right diaphragmatic pleura or right dome of liver.

Much discussion arose regarding the situation of the tumor. The majority ruled that its origin was below the diaphragm, although one of us felt that it lay above. Tumor of the diaphragm *per se* was not considered.

The patient grew progressively weaker and died December 5, 1931.

Necropsy examination (No. 23,669) confirmed the clinical diagnosis of pulmonary tuberculosis. Aside from the tumor to be described below the gross examination showed no features of interest.

The shadow described in the roentgenogram was cast by a tumor lying *between* the leaflets of the right dome of the diaphragm. It measured 12 by 6 by 5 cm., was irregularly rounded and extremely firm. The cut surface showed a tough, grayish-white matrix, mottled by many roughly round hemorrhagic areas most marked near the center (Fig. 3). There was a depression in the posterosuperior surface of the right lobe of the liver,

thus forming a nest into which the inferior surface of the tumor fitted snugly.

Sections were removed from a number of portions of the tumor and the tissues stained by azo-carmine, Heidenhain's hematoxylin and by Mallory's connective tissue stain, in addition to the usual preparations. A definite capsule was present. The bulk of the tumor mass was composed of loose (Fig. 4-*A*) to dense interlacing bundles of fibrocytes that showed little growth activity (Fig. 4-*C*). Many areas had become acellular, varying in density from a delicate, lacy, fibrillar structure to dense, coarse collagen bundles. Some portions of the tissue were necrotic. The areas that had appeared hemorrhagic on gross inspection were seen in section to be masses of well to poorly defined blood channels, closely packed and not well marginated by the fibrous tissue in which they lay. Many of the angiomatous masses were cavernous (Fig. 4-*B*). The fibrous portions were quite vascular *per se* and contained some free hemorrhage. No muscle, cartilage or other tissue elements were present to suggest a teratoid nature of the tumor.

SUMMARY. A case of primary angiofibroma of the diaphragm is described.

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FACIAL DIPLEGIA IN POLYNEURONITIS.*

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FACIAL diplegia may occur in any form of multiple neuritis, although it is most frequently seen in that form of the disease produced by infections, of which there is one with a special tendency to involve the seventh and other cranial nerves. Holmes[1] and Bradford[2] observed cases of this form of polyneuritis during the World War; Yudelson[3] of Chicago and Viets[4] of Boston wrote illuminating articles upon this condition, their papers appearing in 1927. Although polyneuritis is a fairly common condition, involvement of the cranial nerves is rather unusual, however if investigated more often, it would probably be found that the optic nerves are frequently affected. In many of the cases of the infectious

* Read at the meeting of the Section on Medicine, College of Physicians, Philadelphia, April 27, 1931.

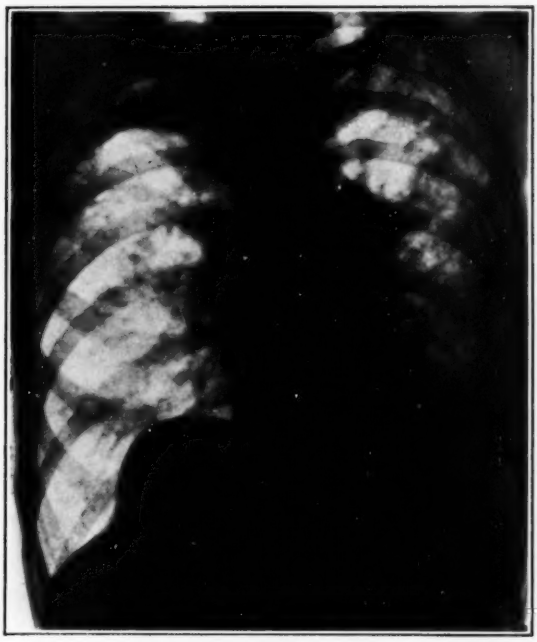


FIG. 1.—Roentgenogram (anteroposterior view). Note tumor mass projecting into right lower lung field.

FIG. 2.—Roentgenogram (right lateral view).

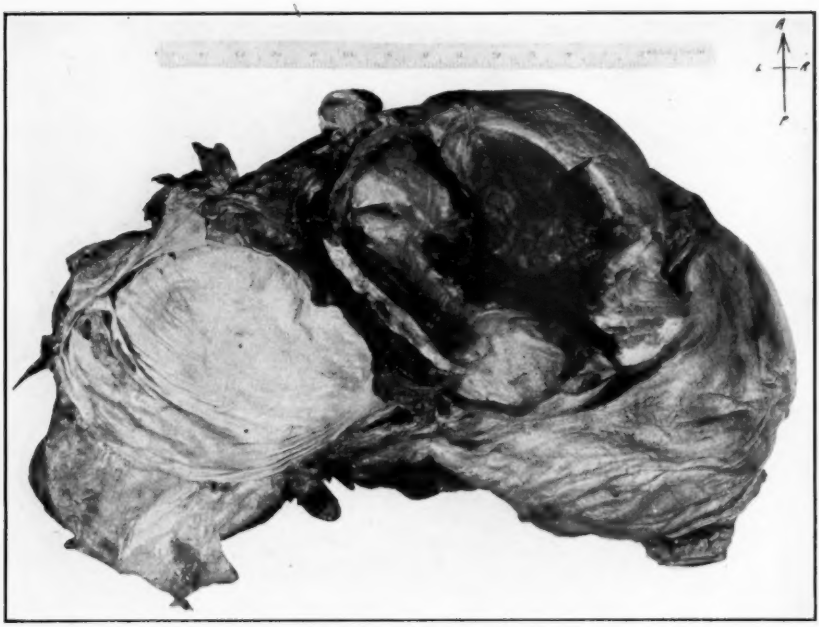
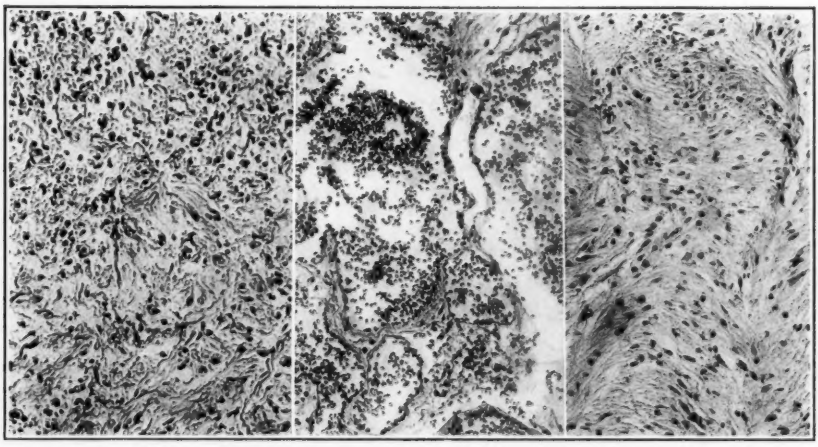


FIG. 3.—Tumor mass (cut open, showing hemorrhagic central zone).



A *B* *C*

FIG. 4.—Histologic structure of tumor: *A*, lacy, fibrillar structure of less dense portion (150 ×); *B*, angiomatous area showing large cavernous blood sinuses (150 ×); *C*, predominating structure of dense interlacing bundles of fibrous tissue (150 ×).

type of multiple neuritis with cranial nerve palsies, there is a distinct ascending element to the paralysis which, beginning in the feet, involves rather rapidly the rest of the lower extremities, then the upper and finally the face. This picture suggests strongly the syndrome called Landry's paralysis. In most of the cases there is a history of a slight illness from 4 days to 6 weeks before the onset of the nervous symptoms. Pain in the back, headache, vomiting and fever from 100° to 101° F. were common symptoms during the febrile stage. Then days or weeks later, in this way resembling very much the palsies that come on after diphtheria, the patient develops tingling and numbness followed by paralysis in 2 or 3 days. In many of the cases the weakness is greater in the proximal segments of the limbs, thus differing greatly from the distribution of the early paralysis seen in the ordinary case of multiple neuritis. In some cases described the patient was totally paralyzed at the shoulders and hips but could move the fingers and toes freely. Facial diplegia was almost constantly seen in Bradford's cases, and he thinks because of the symmetrical weakness it may have been overlooked in others. The sphincters were involved in Holmes' cases, whereas in Bradford's series this did not happen. Complete recovery was often slow, taking as long as 6 months. In Bradford's 30 cases death occurred in 8, from 5 to 12 days after the onset of the paralysis. The cause of death was attributed to weakness of the pulmonary muscles and the diaphragm, although no case of massive collapse of the lungs was found. One of our cases had distinct respiratory embarrassment a few days after the onset.

The microscopic examinations made by Holmes, Bashford[5] and Viets were directed largely to the central nervous system where minute and widely diffuse hemorrhages were present, especially in the spinal cord. Viets found the cells of the seventh nuclei normal in number but almost all with marked structural changes. They were swollen and distorted and many had lost their polygonal form; in addition chromatolysis was extensive with occasional displacement of the nucleus. Cells of the adjacent cranial nerves were ordinary, and sections through the pons and medulla showed no variation from the normal. Throughout the spinal cord in Viets' case the vessels were markedly congested; no mention is made of the study of the peripheral nerves themselves. In Bashford's report the only gross finding of importance was meningeal congestion with some edema of the brain and cord, which Bashford thinks may have been terminal or perhaps associated with respiratory embarrassment. Cross sections showed minute hemorrhages. On microscopic examination the peripheral nerves showed an irregular involvement, most marked in the sciatics. The spinal cord revealed minute and widely diffused hemorrhages in the dorsal enlargement, extensive and advanced interstitial cellularity in both cervical and lumbar

enlargements. The central neural canal showed considerable proliferation of the ependymal cells. The nerve cells of the various tracts, including both the anterior and posterior horns, were irregularly involved. Some of the specimens showed involvement of the posterior roots. Of the portions of the brain examined, all had a slight degree of round cell infiltration, most pronounced around the large antler cells of the cortex, and on the whole greater in the deeper than in the superficial gray matter. There was also pneumonia, and congestion of the liver, spleen and kidneys.

Bashford successfully transmitted the disease from man to monkey and from monkey to monkey by subdural inoculation of an emulsion of the human cord of a fatal case and from the fresh cord of the first monkey to another and later by a pure culture. Wilson[6] isolated the organism and found it to be a minute, rounded or kidney-shaped body, measuring 0.2 to 0.5 μ in diameter; he considers that it shows a marked resemblance to the globoid bodies described in anterior poliomyelitis. From the pathologic reports it will be seen that while extensive studies were made of the central nervous system, comparatively little attention was paid to the peripheral nerves, although the disease is reported as acute polyneuritis. The reports also make it very evident that while the brunt of the affection may be borne by the peripheral nervous system, the central parts do not escape, in fact, they may be more involved than the peripheral.

Patrick,[7] in 1916, reported 3 cases of facial diplegia occurring in the course of multiple neuritis, in one of which there was a history of an acute febrile disorder previous to the onset of the neuritis.

While it is true that most of the cases of polyneuritis complicated by facial diplegia are due to infections, they are not all due to the special infection mentioned above; facial diplegia may occur in any case of multiple neuritis no matter what the cause. For example, one of our cases about to be reported was apparently due to a combination of gonorrhea and pronounced dental infection. Occasionally facial diplegia may occur in the course of multiple neuritis due to alcohol. Before prohibition in this country, we saw on the service of Dr. W. G. Spiller at the Philadelphia General Hospital, a case of multiple neuritis in which facial diplegia occurred. The man had been drinking to excess of an extremely poor grade of whisky.

Report of Cases. CASE 1.—A white, single girl, aged 17 years, with a negative past and family history, was taken ill on December 8, 1928, with an acute cold involving the upper respiratory tract and accompanied by fever and pain in the back of the neck. She was seen by Dr. H. J. Cloud, of Ardmore. Evidence did not exist of pulmonary involvement, and while the patient was uncomfortable she was not seriously ill. Three or 4 days after the onset she complained of numbness in the fingers and toes, and these paresthesias gradually ascended the extremities. With the appearance of the paresthesias in the extremities she noticed what she called

a "stiffness" involving the central part of the face. Diplopia was not present and the eyesight and hearing were normal. She had no headache but vomited twice 2 days after the onset and was delirious on one occasion. The pupils were irregular, the left slightly larger; both reacted sluggishly. The ocular movements and those of the face, palate, tongue and jaws were normal. The neck was slightly stiff and Kernig's sign was present bilaterally. The deep reflexes were lost with the exception of the patellars, which were diminished. Plantar stimulation produced no response, whereas the abdominal reflexes were normal. A blunting of sensation for all forms was present in the distal portions of the extremities. The temperature had ranged from normal to 101° F.

Clinical Course. Two days later she was reëxamined and a double facial palsy and complete paralysis of the palate were noted. The paresthesias were more pronounced in the extremities and distinct but slight weakness was noted in the distal portions. All the deep reflexes were absent and the sensory loss was more profound and covered a wider area in the extremities, although sensation in the face was normal. She was transferred to the University Hospital on December 16, 1928, and Dr. Alfred Stengel saw her in consultation. The nose and throat examination at this time revealed that the left vocal cord was almost motionless while the right had only fair motility. A considerable amount of pus was present in the nose and the palate was congested, glazed and covered with thick, tenacious mucopus. By January 4, 1929, laryngeal motility had returned to normal and the pharynx showed evidence of returning function. A Roentgen ray of the sinuses revealed clouding of the frontal and ethmoids on both sides; some thickening of the maxillary mucous membrane existed, especially the left; the sphenoid cells were negative. The Wassermann reaction, examination of the urine and a blood culture were negative. A culture from the nose and throat showed a heavy growth of staphylococci and streptococci but no Klebs-Loeffler bacilli. The temperature was elevated during the first 3 weeks of her stay in the hospital, but was usually below 101° F. Quite severe pain developed in the feet, which also became weak, more particularly in the extensors, and very tender to pressure. The hands also were weak and showed moderate wasting in the interosseous spaces. During the first 24 hours after her admission to the hospital distinct respiratory impairment occurred, but subsided. Moderate depression and intense insomnia were prominent symptoms for the first 3 weeks. She was discharged from the hospital on January 18, 1929, 44 days after the onset, in a greatly improved condition. Subsequently she made a complete recovery with the exception of slight persisting weakness with contracture of the lower part of the right side of the face. The deep reflexes returned much more quickly than after the ordinary case of multiple neuritis and became exaggerated, although positive signs of pyramidal tract involvement were never discovered.

A lumbar puncture was not done.

Comment. This patient had what seemed to be an acute cold complicated by ethmoid and frontal sinus disease. In addition to the ordinary signs of polyneuritis she had a double facial palsy, a complete paralysis of the palate, paralysis of the left vocal cord and weakness of the right. In addition she showed rather marked depression and insomnia. During convalescence the deep reflexes returned rather quickly and became exaggerated, although Babinski's sign was never found. The quick return of of the reflexes and later their exaggeration, we believe, points to the involvement of the pyramidal tracts either in the cord or higher up. It is most likely that the cranial nerve palsies in this case were central in origin rather than peripheral.

CASE 2.—A white, married woman, aged 41 years, was admitted to the neurologic service of the Episcopal Hospital on May 23, 1924. She had had 6 children, 5 of whom were living and well; she had had one stillbirth. Her last child was born 10 weeks before the onset of her present trouble; the birth was normal. The question of her use of alcohol was thoroughly investigated and it can be asserted positively that she did not use the drug at all. She did not have an acute febrile disorder after the birth of her child. Her chief complaints were numbness, tingling and weakness in the hands and feet and inability to move the face. Her trouble dated back 4 weeks when paresthesias appeared in the fingers and toes and, while gradually spreading upward in the lower extremities, did not go higher than the fingers in the upper extremities. A week after the onset she had difficulty in walking because of weakness. Her condition slowly became worse and one week before admission, or three weeks after the onset, she became confined to bed, and shortly thereafter her face became "stiff" and paralyzed. For the first week she also had diplopia, the objects being placed side by side. She had no sphincter disturbance.

Examination. The pupils were equal, regular and reacted well to light and in accommodation. Except for a weakness of the right internal rectus muscle all the ocular nerves functioned well. Double vision was present when the patient looked to the left. A complete bilateral facial palsy was present with the loss of contraction of the muscles to faradism. The breath was heavy and offensive. The tonsils were small and buried and pronounced redness of the anterior pillars was noted. The lungs, heart and abdomen were normal. All of the deep reflexes were absent, the plantar reflexes were normal, but the abdominals could not be obtained. Lasêgue's sign was present on both sides. Slight contracture in flexion was present at the knee joints. Bilateral foot drop was noted and a generalized moderate weakness was present in the muscles of the lower extremities and in the uppers below the elbows. Pressure along the course of the nerves and laterally to the feet produced marked pain. She had no trouble in chewing or swallowing. Mentally she was irritable but showed no evidence of a psychosis. A Roentgen ray of the teeth showed what was described as a "huge bone abscess" involving the upper left central and lateral incisors and canine and a root abscess about the upper right canine. A number of examinations of the urine showed hyalin and granular casts and on two occasions the urine showed many leukocytes. Blood chemical studies, routine examination of the blood and spinal fluid (with the exception of the colloidal gold curve which was 4432110000) and a culture of the throat for Klebs-Loeffler bacilli were all negative. A gynecologic examination revealed a chronic gonorrheal endocervicitis and urethritis. The vaginal and cervical smears showed many Gram-negative diplococci, both intra- and extracellular.

This patient gradually improved so that by August 4, 1924, she was discharged in good condition. The power had completely returned in her extremities and in her face, although she could not close the eyes tightly.

Comment. This patient was reëxamined in October, 1930, and was entirely well except for weakness in closing the right eye, and the loss of the deep reflexes. She was never as acutely ill as our first case. We believe the etiologic factors here were gonorrhea and dental infection. It is likely that most of the symptoms in this case were due to peripheral nerve lesions, although the colloidal gold curve pointed to central involvement.

CASE 3.—A colored female, aged 23 years, was admitted to the neurologic service of the Philadelphia General Hospital, January 3, 1928, with the chief complaint of inability to walk. She was perfectly well until the latter part of August, 1927, when she began to suffer with severe, continuous headaches accompanied by chills and fever. In the middle of September

she noticed that she was extremely nervous and had pains in her joints. About the middle of December her face "swelled," became numb, and felt as if paralyzed. Then her legs became stiff and weak. Finding that she frequently fell, she remained in bed. Paresthesias developed in the hands, which at this time became paralyzed. Pain has been most severe in the hands, feet, knees and the elbow joints.

Her past medical history suggests that she was suspected at least to be syphilitic, because she was given 8 injections of neoarsphenamin at a hospital in January and February of 1927. Since that time she has had 2 negative blood Wassermanns. In addition there have been recurring attacks of tonsillitis for a period of 2 years, and diphtheria was contracted 4 years ago. One child born in March, 1927, is living and well. The patient has never had a miscarriage.

Examination. A facial diplegia with inability to pucker the lips, laugh, close the eyes tightly or wrinkle the forehead was found. The pupils were slightly irregular, the right being larger than the left; the eyes otherwise were normal. The tonsils were large, cryptic and diseased. The extremities showed bilateral foot- and wrist drop with inability to perform any motion whatsoever below the shoulders and hips. All of the deep reflexes were lost. No disturbance of sensation existed except extreme tenderness upon compression of fingers and toes and of muscles of arms and legs.

The *laboratory examinations* revealed a negative Wassermann in the blood and spinal fluid. The colloidal gold curve was 0122233333; there were 21 cells per c.mm. of spinal fluid, and a trace of globulin. Blood chemical studies, blood count, throat smears and culture for Klebs-Loeffler bacillus, and urinalysis were all negative. A cervical smear was negative for the gonococcus. The optic disks showed pallor of the temporal sides. Reactions of degeneration were present and widespread in both the upper and lower extremities and in the face.

Clinical Course and Outcome. This patient remained in the hospital for 10 months. At the end of the second month her tonsils were removed; they were found to contain several pockets of pus. Following their removal the temperature, which had been slightly elevated, became normal and remained so. Power began to return in the face about 6 months after admission to the hospital. When she left she had slight movement in her fingers and toes but could not stand, walk, nor feed herself. Two years after the onset power had improved in her lower extremities sufficient to enable her to stand and walk. She was reëxamined on March 11, 1931. The face had entirely recovered. All movements were possible in the upper extremities, but there was some limitation of the motion at the metacarpophalangeal joints due to ankylosis. All movements in the lower extremities were possible, but extension of the toes and feet was not normal and the gait was of the steppage type. The muscles had not regained their full contour, but had improved greatly over the condition they were in when the patient left the hospital.

Comment. We believe the cause of this woman's nervous disorder was an infection which probably was present in the tonsils; following their removal the temperature dropped to normal and remained there. No evidence of infection could be found in the blood or endocardium, and while there may have been a blood stream infection at the onset, laboratory evidence of this could not be found. Careful cultures of the throat and tonsils were made in this as well as the others for Klebs-Loeffler bacillus.

On one occasion in the nervous wards of the Philadelphia General Hospital we saw 2 cases of multiple neuritis who had done poorly for weeks. Cultures of the throat revealed Klebs-Loeffler bacillus

in both cases, and after injections of diphtheria antitoxin and the removal of the tonsils both cases recovered.

Discussion. It is quite clear from the examination of cases of so-called polyneuritis complicated by cranial nerve palsies or not, and from a review of the literature on the subject, that there are many cases in which the central nervous system is involved as well as the peripheral. As far back as 1898, Mills[8] proposed the term neuronitis for cases of this sort, although he said that it had an unnatural sound, even to a neurologic ear. Kennedy[9] and Brock and Ivimey[10] have described cases under this title. In the discussion of the paper, "On the Causation and Symptomatology of Multiple Neuritis," by T. Grainger Stewart,[11] S. A. K. Wilson said that the term "multiple neuritis" was a misnomer in many instances. He proposed that if no sensory symptoms were present the term neuronitis should be used, but if the lesions were multiple polyneuronitis would be appropriate.

Under the title of "Acute Ascending Paralysis Among Troops," Casamajor[12] described 2 cases comparable in many ways to those described by Bashford and others, and for which Casamajor hesitatingly proposed the term "Acute Infective Meningo-myeloneuritis."

As "Myeloradiculitis," Strauss and Rabiner[13] wrote about a group of cases that might readily fit in with those that have been taken up in this paper. Most of their cases had had infections involving the upper respiratory tract before the onset of the symptoms indicative of the involvement of the roots and cord. The most extraordinary thing about these cases was the rapid improvement. Two French authors, Guillain and Barré, described in 1916 a syndrome with symptoms indicative of lesions of the spinal roots and peripheral nerves, and in some instances with signs suggesting spinal cord involvement. In fatal cases they found inflammatory lesions of the nerve roots, spinal ganglia, spinal cord and peripheral nerves.

Conclusions. Patients suffering from multiple neuritis occasionally have cranial nerve involvement, and the cranial nerve most frequently involved is the seventh. This may occur in ordinary multiple neuritis, which, as is well known, may be due to almost any toxic or infectious condition. However, there is a special neurotropic infection which may be closely allied to that of epidemic encephalitis or poliomyelitis, and which may involve not only the peripheral, but also the central nervous systems. In this condition cranial nerve palsies are especially likely to be found, and when present are probably more often due to involvement of the central than of the peripheral nervous system. The 3 cases which form the basis of this paper all occurred in women and all were due to infections. Cases 1 and 3, especially 1, conform rather well to the infectious type of polyneuronitis. While Case 2 was also infectious, it seemed to be due to a combination of gonorrhea and dental infection.

Confusion exists in the nomenclature because of the various headings under which this disease has been described. Due to the fact that the organism has a tendency to localize in different parts of the nervous system, individual investigators have given various names to the disease, depending upon what particular part was involved pathologically in their cases. Of all of the terms suggested to date, the most descriptive is that of Mills, "neuronitis."

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CEREBELLAR APOPLEXY.*

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Hemorrhage and thrombosis are infrequently limited to the cerebellum. Postmortem observations indicate an impressively low incidence of cerebellar apoplexy. The purpose of this presentation is to report 10 cases of hemorrhage in the cerebellum only, and to describe the clinical syndromes with their pathogenetic relationships. Two cases coming to autopsy at the Minneapolis General Hospital during 1930 stimulated a search of the hospital files, which yielded records of but 3 previous cases verified postmortem. A review of the reports on all cases of cerebral hemorrhage on file in the Department of Pathology, University of Minnesota, lead to the finding of 5 more cases. Frequency as indicated by postmortem records is shown in Table 1.

Table 1.—Frequency of Cerebellar Apoplexy.

	Number of cases.	Per cent.
Autopsy records in the Dept. of Path. from 1897 to 1931	17,257	
Cases of cerebral hemorrhage	1,112	6.5
Cases of cerebellar hemorrhage without coincidental cerebral hemorrhage	10	0.0058

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Case Abstracts. CASE 1.—A–951, male, negro, aged 60 years, admitted to Minneapolis General Hospital August 15, 1909, complaining of a pain on the movement of his right leg and exhibiting evidences of senility. He had been unable to walk for 2 years. Died August 28, 1909. No other clinical data available. *Autopsy:* On section of the cerebellum, in right lobe near the worm, there is a firm grayish-yellow caseated mass which projects toward the right and measures about 1.5 cm. in diameter and 5 cm. in length. This is surrounded by a grayish-white thickened wall and in the middle of the pulp of the right lobe there is a hemorrhagic area containing a thick, dark, firm clot about 2 cm. in diameter. Vessels at base of brain are thickened and tortuous. Microscopic examination shows a large area of necrosis surrounded with thick capsule with connective tissue hyperplasia, dense lymphoid cell infiltration and occasional giant cells. *Comment:* Though available clinical notes are limited, the autopsy findings indicate that clinical course continued over 2 years and that death was not caused directly by the hemorrhagic lesion, which was well encapsulated.

CASE 2.—A–14–234, male, aged 51 years, baggageman at Union Depot, admitted to St. Paul City and County Hospital November 18, 1914. Except for slight cold and pain in back of head, was well until November 11, 1914. Then he became too weak to work. Headache developed and vomiting persisted. On November 16, was found unable to talk; appeared drowsy. Breathing labored at intervals. Did not regain consciousness in the hospital. Examination on November 18, revealed thickening of all palpable arteries. Knee jerks, 2 +; Babinski and ankle clonus, bilateral; Achilles reflex, present on left side only. Exitus November 26, 1914. *Autopsy:* A large blood clot, 2 cm. in diameter, is found in left lobe of cerebellum. Circle of Willis and the other cerebral arteries show marked nodular thickenings. *Comment:* Hemorrhagic focus is illustrated in Fig. 1. Onset with headache localized in occipital region, and vomiting and prostration, without loss of consciousness for the first few days, is quite typical.

CASE 3.—A–17–56, male, aged 73 years, admitted to Minneapolis General Hospital January 15, 1915, with right hemiplegia of spastic type. Clinical note, March 7, 1917: "I feel about all in;" said both his legs were jerking. He went to bed. At 11.00 P.M. he began to vomit violently. Did not speak, but could help himself. Fell asleep and this morning was found in stupor. Protrudes tongue slightly. Unable to answer questions. Moans at times, especially when touched. Coughs. Pulse irregular, blood pressure 165 systolic and 108 diastolic. Left pupil slightly larger than the right and slightly irregular in outline. Light reflexes absent. Right eye deviates outward. Right face smoother than left, right corner of mouth somewhat depressed. Right arm and leg very spastic. Right knee jerks rather active, left feeble. Babinski great toe sign positive on right, doubtful on left. Right abdominal reflex absent, left feeble. Wassermann, negative. March 8, 1917, bloody spinal fluid removed under increased pressure. Pulse quite regular, 98, until 8.00 P.M. Breathing became labored and patient died the next day. *Autopsy:* Upon reflecting dura considerable quantity of bloody fluid is found to be present in the pia-arachnoid space. Upon sectioning the brain, all of the ventricles are filled with bloody fluid. There is a large hemorrhagic lesion occupying the center of the cerebellum. *Comment:* Patient presented an old cerebral hemiplegia for which he was receiving custodial care. Onset of cerebellar hemorrhage indicated by violent vomiting. Lesion penetrated cerebellar parenchyma to fourth ventricle within several hours after onset, followed by coma and early death. Signs of former cerebral lesion complicated the neurologic picture.

CASE 4.—A–20–25, male, aged 55 years, admitted to Minneapolis General Hospital January 20, 1920, having been found unconscious. He had always been well previously. He did not regain consciousness at the

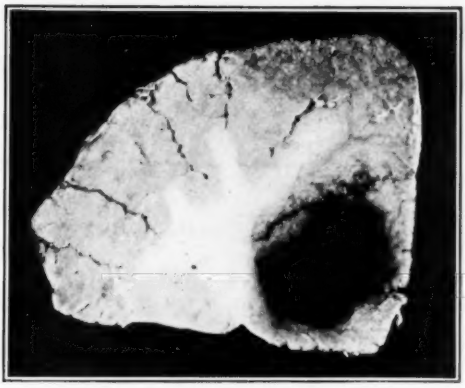

FIG. 1.—Circumscribed hemorrhagic lesion, Case 2.

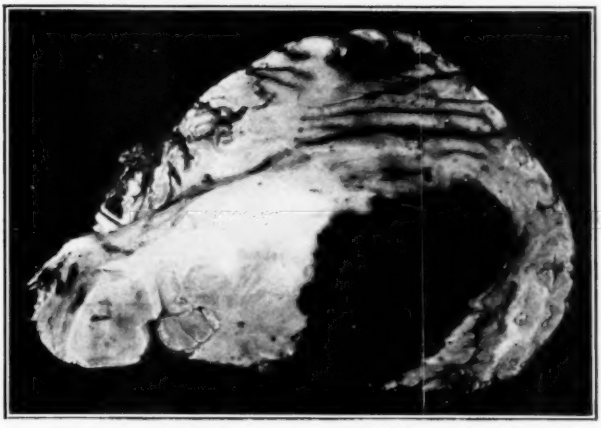

FIG. 2.—Massive hemorrhagic lesion communicating with subarachnoid space, Case 7.

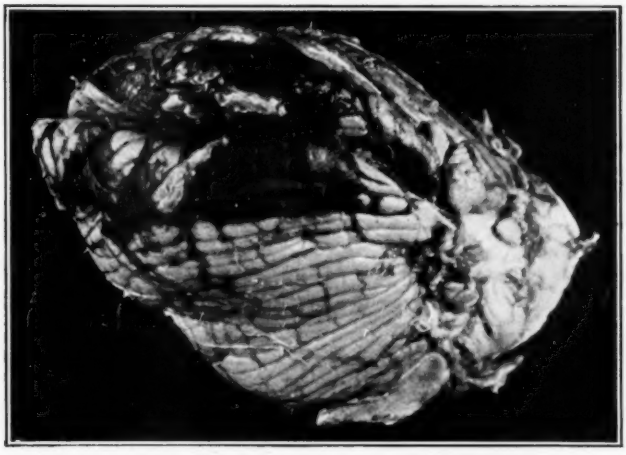

FIG. 3.—Hemorrhagic extravasation to cerebellar cortex, Case 7.

hospital and died 14 hours after admission. *Autopsy:* On removing brain 15 gm. of clotted blood are found escaping from left cerebellar fossa. Sectioning reveals large hemorrhage into left cerebellar lobe with softening of the parenchyma, leaving only a shell, less than 1 cm. in thickness, surrounding the hemorrhage. The blood clot extends into the fourth ventricle. Blood tinged fluid is present in both lateral ventricles. Masses of blood clot are present in anterior horns. Bloodvessels show extensive nodular thickening; the greatest involvement is along the middle cerebral arteries and the circle of Willis. Microscopic examination shows softening and hemorrhage; many esosinophils in parenchyma around hemorrhage. *Comment:* Here we have represented the more fulminating type of syndrome. The lesion, a massive one, allowed no interval to observe cerebellar signs uncomplicated by neighborhood involvement.

Case 5.—A–20–362, male, aged 60 years. At midday, September 30, 1920, he complained that he felt very sick. In going to his room he fell over a trunk. The housekeeper helped him into bed; patient could use but one arm. At 3.05 the following morning he was found dead. *Autopsy:* There is little blood over the base of the brain which has escaped from a tear in the left lateral cerebellar hemisphere. The central part is occupied by a large blood clot. The hemorrhage communicates with the cavity of the fourth ventricle, filled with blood. Clotted blood found also in the aqueduct of Sylvius and in the third ventricle, and lateral ventricles contained fluid blood. The arteries over the base of the brain show no changes except in the posterior cerebral and cerebellar branches. These contained a large number of yellowish thickened intimal areas. Microscopic examination of organs shows hyalin degeneration in kidneys, spleen, etc. *Comment:* Quite similar to Case 4, except that several hours intervened during which patient was conscious. During this interval the signs of an acute cerebellar attack are suggested by the available record of complaints.

Case 6.—A–26–1113, male, aged 65 years, merchant, was found dead. He was last seen alive in the afternoon of December 17. It is reported that there had been recent nose bleeds. *Autopsy:* There are blood clots in the subdural space of the left posteranial fossa and some free blood in the subarachnoid space over the base. There is hemorrhage and softening involving the entire central portion of the left cerebellar hemispheres with a tear of 6 cm. in diameter across the free surface. There is marked thickening and beading of all the arteries over the base of the brain. *Comment:* Another illustration of quite sudden death caused by hemorrhage into the cerebellum.

Case 7.—A–28–223, male, aged 62 years, railroad laborer, admitted to St. Paul City and County Hospital July 6, 1928, complaining of dyspnea, headaches, pain in cardiac region and in his back, swelling of his hands, feet and legs—signs of cardiorenal failure. On afternoon of day following his admission, patient became very restless, severe headache developed and coma set in early that evening; his respirations became very labored and stertorous in character. He died at 1.30 p.m., July 8, 1928. *Autopsy:* There is an area of hemorrhage over one-half the surface of the right lobe of the cerebellum, and on cut section there is found to be a massive hemorrhage in the right lobe of the cerebellum which has destroyed about one-third of the substance, and there is hemorrhage about 2 cm. in diameter in the left lobe of the cerebellum. The cerebral vessels show little evidence of sclerosis. *Comment:* Patient developed first signs of acute cerebellar involvement on the second day in the hospital. Restlessness and headache were followed in 5 hours by coma and early death, probably due to the hemorrhagic penetration through cerebellar cortex. This is illustrated in Fig. 2.

Case 8.—A–30–45, male, aged 62 years, admitted to Minneapolis General Hospital March 17, 1930. History of high blood pressure for some time.

There had been attacks of indefinite type, supposedly related to high blood pressure, which made him unable to hold his position of night watchman. He rather suddenly complained of heat and rose from his chair, then fell "into a heap." He had not become unconscious. Attempted erect posture several times but failed. He complained of headache, dizziness and vomiting. Heart was enlarged to the left. Blood pressure was 205 systolic and 120 diastolic. Neurologic examination at time of admission revealed pupils equal and normally reactive and a divergent squint. Mouth was pulled very slightly to the left side. Speech was mumbling and slurring. Tongue deviated slightly to the right. Abdominal reflexes were more active on the right side. Muscle power in right arm seemed slightly reduced. No other signs of palsy; no sensory disturbances present. Reflexes presented no other changes. Vertigo persisted. Patient became more drowsy and continued to vomit. Spinal puncture brought forth very bloody fluid under marked increased pressure. Temperature subnormal on admission, but it rose gradually to 103.8° F. prior to death. Blood pressure 180 systolic and 100 diastolic on second day. Pulse range from 70 to 120. Respiration 22, gradually rose to 32. Totally unconscious on 5th day, died on the following day. *Autopsy:* Lateral and third ventricles markedly distended. Right caudate nucleus presents a small pigmented cyst ½ cc. in diameter. The cerebellum is greatly softened and enlarged. It is pressed firmly against the aqueduct of Sylvius and causes apparently complete collapse of the aqueduct. Section through the cerebellum reveals large hemorrhage occupying most of the right lobe and about one third of the left lobe. There is a small amount of blood beneath the arachnoid in its inferior surface. The vessels at the base of the brain show no gross evidence of disease, although some in the peripheral areas are moderately atheromatous. *Comment:* Clinical course was sufficiently protracted to portray a fairly typical cerebellar syndrome. Brunt of lesion suffered by right lobe, but vermis and part of left lobe became involved, presumably by fairly rapid extension. The penetration through cerebellar cortex and pressure of the tumorous mass toward the brain stem explain the early fatal termination.

Case 9.—A–30–735, 1 month old, patient of Dr. M. J. Lynch, born at St. Mary's Hospital. Delivery normal. Nothing of note until the 10th day, then began projectile vomiting and loss in weight. Child vomited after nearly every feeding for the following 3 days. At first vomiting was projectile in character. *Autopsy:* The right lobe of the cerebellum is larger than the left, pushing the tentorium upward. The lateral ventricles are markedly distended with fluid. Cut section of the cerebellum shows a large clot of blood in the right lobe with softening in the adjacent areas. Other postmortem findings: (1) internal hydrocephalus; (2) terminal bronchopneumonia. *Comment:* Though meningeal bleeding in the posterior fossa is relatively frequent in the newborn, massive hemorrhage into the cerebellum is decidedly rare. In this case of an infant, projectile vomiting began on the 10th day, prior to which date attending physician had noted nothing irregular. Signs of increasing intracranial pressure were evident, producing death 3 weeks after onset of first symptoms of cerebellar attack. No developmental anomaly could be established.

Case 10.—A–30–1252, female, aged 42 years, admitted to Minneapolis General Hospital August 22, 1930, in coma with Cheyne-Stokes respiration. The day previously patient began to complain of headache. She gradually became weaker and comatose 2.00 A.M. the following morning. Pupils pin point, did not react to light. Heart enlarged to left, systolic murmur heard at apex. Neurologic examination revealed palsy in right arm and leg. She expired at 11.20 the morning of the same day. *Autopsy:* Brain reveals an area of recent hemorrhage and softening, 2 cm. in diameter, in

the left lateral lobe of cerebellum, involving the area of the dentate nucleus. No degeneration in the cerebral arteries. *Comment:* Pathogenesis not determined. Nothing of a neoplastic character or developmental anomaly was noted.

TABLE 2.—COMPOSITE SUMMARY OF CASES 1 TO 10, SHOWING AGE, SEX, DURATION, LOCATION AND EXTENT OF HEMORRHAGE, AND STATE OF BLOODVESSELS.

Age.	Sex.	Duration.	Area chiefly involved.	Extent of hemorrhage.	Degeneration of cerebral vessels.
(1) 60	M.	2 (?) yrs.	Right lobe	Circumscribed	Yes
(2) 51	M.	15 days	Left lobe	Circumscribed	Yes
(3) 73	M.	3 days	Vermis and both lobes	Into ventricular system	Yes
(4) 55	M.	14 hours	Left lobe	Into ventricular system	Yes
(5) 57	M.	15 hours	Left lobe	Into ventricular system	Yes
(6) 65	M.	Found dead	Vermis and both lobes	Into subdural space	Yes
(7) 62	M.	1 day	Both lobes	Into subdural space	Slight
(8) 62	M.	6 days	Right mainly, vermis and left also	Into subdural space	Yes
(9) 1 mo.	M.	20 days	Right lobe	Circumscribed	No
(10) 42	F.	1 day	Left lobe	Circumscribed	No

Historical. Sedillot[1] of Paris, France, was the first to report a case of cerebellar hemorrhage in 1813. Huss reported the first case in Sweden in 1842; Dunn in the British Isles, 1849; Schulz in Germany, 1854; and de Nasca in Italy, 1863. Childs[2] is the first American author. His case was that of a girl, aged 19 years, whose symptoms developed while amusing a child by shaking her head violently. Carion[3] published a report of 7 cases of hemorrhage, and 1 of softening; he referred to previous publications by well known 19th century French neurologists: Andral, Hilliaret, Brown-Sequard, Ollivier, Raymond and others. His clinical observations were remarkably comprehensive and precise. Mills[4] demonstrated a brain presenting hemorrhage in the cerebellum, and by extension into the ventricular system, at a meeting of the Pathological Society of Philadelphia in 1889. Starr[5] could find in the literature up to that time 27 cases diagnosed postmortem. While arteriosclerosis was recognized as a predisposing factor by early authors, other etiologic factors as trauma, epileptiform seizure, syphilis, diabetes, aneurysm and acute infection, referred to below, were made clearer in more recent times. However, the literature shows a notable paucity of reports concerning apoplectiform cerebellar disease. This applies even more to thrombosis than to hemorrhage. Though relatively small foci of softening are not infrequently encountered in postmortem examinations, the more massive and isolated thrombotic lesion producing the unique clinical syndrome of cerebellar

involvement followed by death is still more uncommon than isolated hemorrhage.*

Symptomatology. Three types of syndromes characterize the symptomatology and course: (1) Fulminating; (2) grave; (3) benign.

In the first type there are no premonitory signs or, at the most, patient utters a brief cry and places his hand at the nape of the neck. He falls over and death is practically instantaneous. Some patients are found dead. In the present series of cases reported there was but one belonging to the fulminating type.

Cases of the second type have an onset less abrupt. Premonitory symptoms are frequently determinable. These are severe occipital pain, sensation of turning, nausea, vomiting, increasing feeling of prostration and inability to stand upright, irregularity of pulse, labored breathing and rotation of the head away from the side of lesion. Pupils are contracted and fixed. Rigidity of neck and Kernig's sign may be present.[6] Location and extent of the hemorrhagic lesion are not uniform, hence the rapidity and degree of development of symptoms vary. Impairment of consciousness may be noted within a few minutes or may not be present until some hours or more later. Sometimes relatively early drowsiness is followed by lucidity until terminal coma sets in. Spinal puncture yields a bloody fluid. Inasmuch as the brunt of the lesion is more often confined to one lobe, it is possible to make out, in patients who are able to coöperate, the syndrome of unilateral localization. In addition to signs of dyssynergia involving arm and leg of the side of the lesion, one notes in some cases a dysarthria, and nystagmus is present as a rule. Divergent squint is frequently observed. Asynergia, nystagmus and vertigo have the tendency to persist while the patient is conscious. Signs of pyramidal tract involvement are notably absent. Tonic or clonic convulsive attacks occur infrequently. Labored breathing, irregular and rapid pulse, rise in temperature and coma precede exitus.

In cases of the benign type we find the premonitory signs mentioned above less constant and less pronounced. Quite likely, a goodly number of these cases are undetected antemortem. If the expected circumscribed lesion is relatively small, the cerebellar symptoms are minimal. The larger lesion produces signs of increasing tumor in the posterior fossa ending in early death.

In reviewing the symptoms we can note that the fulminating syndrome offers practically nothing characteristic of the cerebellum itself, nor even of the posterior fossa. Antemortem localization is practically impossible in all these cases.

Referring to the second or grave syndrome, a variable train of

* Following the writing of this report I had a case of cerebellomalacia without major signs of brain stem or cerebral lesion which came to autopsy at St. Mary's Hospital.

symptoms become manifest to the clinician. Posterior fossa insult is clearly indicated. Headache, vertigo and asthenia at the time of onset are attributable to initial circulatory disturbance. Irregularity of pulse and respiration signify neighborhood medullary involvement. Nystagmus and deviation of the eyes suggest an irritative or destructive process in the roof nuclei or vestibular fiber tracts. Rigidity of the neck and Kernig's sign, if present, point to menigeal irritation. Loss of power in individual muscle groups and objective sensory disturbances indicate, if present, neighboring brain stem involvement. Focalized cerebellar involvement is shown by impairment of the fundamental cerebellar function: synergia, defined as "the power by which movements more or less complex, but functionally definite, are associated in special acts."[7]

Disturbances of equilibrium, incoördination, dysdiodochokinesia, dysmetria, lateral nystagmus, dysarthria, turning of head away from the affected side, noted in some cases of cerebellar hemorrhage, belong to the asynergic category. In the grave type the vermis does not escape involvement. Extracerebellar signs are, after all, prominent. Many of the premonitory signs point to neighboring posterior fossa structures, whereas the late signs include those of irritation and distention of the ventricular and subdural cavities. McCollum[8] calls attention to hyperglycemia as a possible symptom of grave cerebellar hemorrhage.

The benign type tends rather to offer a possible recognition of the so-called pure cerebellar syndrome. Here a varying picture of dyssynergia, uncomplicated by neighborhood signs, tends to obtain, for the hemorrhagic lesion is small and circumscribed. Impairment of synergia persists in these cases. This persisting impairment is suggested in Case 1. It is indicated in Schaller's case.[9]

Pathogenesis. Bloodvessel disease is the common primary factor. Arteriosclerosis with hypertension is found in a majority of the cases. Syphilitic arteritis is not infrequently accountable. Diabetes may explain a hemorrhagic lesion in the cerebellum in young persons.[10] Birth trauma producing a rupture of the tentorium cerebelli near the anterior extremity of the strait sinus is followed by cerebellar venous hemorrhage. This instance is suggested in Case 9. Postnatal traumatic hemorrhage caused by direct injury to the cerebellum is extremely rare. An illustration of hemorrhage into cystic cavity following head trauma is indicated in Hird's case.[11] André-Thomas[12] reported 2 cases of hemorrhage following head injury. There were no others in a series of 4076 head wounds observed during the World War. There have been but few cases resulting from injury sustained in boxing and in violent exercising, *e. g.*, the case of Hoffman.[13] Aneurysmal hemorrhage is also most rare; Hamilton[14] found 4 in a series of 86 cerebral aneurysms. Acute arteritis developing in the course of an acute infectious dis-

ease is known to have produced cerebellar hemorrhage. Epileptiform seizure figured in a patient without arterial disease, in the case reported by Thyne[15] and was followed by the grave type of cerebellar hemorrhage. Alcoholism and epilepsy were associated in Boldt's case.[16]

An explanation for the rare incidence of cerebellar hemorrhage is suggested by the liberal anastomosis of bloodvessels of both sides in the median of vermis; this area is most rarely the focus of vessel rupture. Lacunar disintegration, while relatively common in the senile cerebrum, is much less pronounced in the cerebellum. The artery to the dentate nucleus resembles the lenticulostriate artery of the cerebrum in that it is as a rule involved in cerebellar hemorrhage; this artery is a branch of the external branch of the superior cerebellar artery. Multiple hemorrhagic areas have been noted. A small and relatively benign hemorrhagic focus or softening may, of course, be followed after an interval by a severe hemorrhage.

Syndrome of Cerebellar Apoplexy. It is apparent from the foregoing that it is not possible to define one syndrome which will characterize all cases. As a general rule it can be stated that in those cases where recognition of identifying symptoms and signs is impossible, the course is brief and fulminating. In the absence of coma, correct antemortem diagnosis is possible.

Premonitory signs: severe occipital pain, sensation of turning, nausea, vomiting and feeling of intense prostration, point to cerebellar localization. Signs pointing to the nonequilibratory, as well as to the equilibratory dyssynergias, are typical. The absence of sensory and pyramidomotor involvement, and retention of mental integrity at time of onset, is characteristic.

Summary. 1. Postmortem findings and clinical notes of 10 cases of hemorrhage into the cerebellum only are reported.

2. The history, symptomatology and pathogenesis of the condition are discussed.

3. Postmortem statistics indicate an extremely low incidence rate for isolated cerebellar hemorrhage, and even more so for thrombosis.

4. Clinical syndromes of cerebellar apoplexy are described and diagnostic criteria outlined.

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SPONTANEOUS BILATERAL PNEUMOTHORAX.

WITH REPORT OF A CASE AND REVIEW OF LITERATURE.

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SPONTANEOUS bilateral pneumothorax is very rarely observed, although probably it occurs more frequently than is reported. Generally, it is a complication of evolutive pulmonary tuberculosis, though it may follow several other conditions. Less than 50 cases have been reported in the literature.

Owing to the rarity of spontaneous bilateral pneumothorax and to the fact that American literature on this subject is rather meager, it should be of interest to report the following case to which is appended a short summary of the literature with bibliography.

Case Report. On July 16, 1929, Dr. R. S. Breakey, Monticello, N. Y., referred to the Loomis Sanatorium a white man, aged 27 years, for consultation regarding a pneumothorax involving his left hemithorax. About the end of June, 1929, he developed a common cold while in the pursuit of his occupation as traveling salesman. The symptoms were pharyngeal irritation, slight nasal catarrh and later a rather irritating cough with slight frothy expectoration. There was no sudden pain nor feeling of weakness, faintness, dyspnea nor tightness in the chest. His appetite was good; he did not feel feverish nor unduly fatigued. He remained active, but his symptoms gradually got worse; his cough and expectoration increased and the latter became quite "phlegmy" in character; fatigue became more noticeable and in the evening he felt flushed and feverish. On June 28, 1929, he went to bed and called in a doctor, who found his temperature 102° F. (mouth). After a week of bed rest his temperature became normal and cough and expectoration diminished. On July 6, 1929, he first became conscious of a dull pain in his left midchest anteriorly. The pain was aggra-

vated on deep breathing but was not accompanied by conscious dyspnea. He was in bed at the time and does not recall any undue strain. Dr. Breakey suspected spontaneous pneumothorax and a Roentgen ray examination established the diagnosis. Between June 25 and July 16, 1929, he lost about 10 pounds in body weight. At the time of examination on July 16, 1929, he felt fair; appetite and digestion were good and he slept well. He had cough and a moderate amount of muco-purulent sputum. He was not dyspneic. He had a dull pain over the left anterior midchest which was aggravated on movement, but not on deep breathing.

Of interest in his past history was an undue susceptibility to colds dating from childhood. The symptoms were cough and expectoration, malaise and slight fever; never any blood spitting. Since 1926 these attacks were accompanied by pain in the chest. The pains were not very severe and were of a dull, rather than of a sharp stabbing character, and localized over the upper anterior quarter of both lungs; during a given attack the pain was chiefly unilateral, but the same side was not always involved and he could not say which side was more frequently affected. In 1924 he had influenza; the symptoms were fever (maximum 103° F., mouth), malaise, general aching over the body, cough and expectoration, but no hemoptysis. He was in bed 3 or 4 weeks and convalescent for a month. There was no history of allergic diseases. He married in February, 1924; his wife is in good health; there are no children.

Physical examination showed a moderately undernourished and frail-looking man (weight 54.6 kg.—standard weight 73.9 kg.), slightly stooped, rather nervous apprehensive look, breathing easily. His fingers were slightly clubbed and the nails showed longitudinal striations but no pitting of the nail beds. The thorax was long and slender and movement on the left side was less than on the right. There was no bulging and the only visible pulsation was in the left fifth interspace internal to the nipple line.

Over the right lung the percussion note was of good quality. Breath sounds were slightly exaggerated throughout. Below the eighth spine, extending to the posterior axillary line at the tenth spine, there were fine and medium râles following cough. Over the left lung the percussion note was hyperresonant throughout, more so in the axilla. Breath sounds were diminished to suppressed throughout, anteriorly; audible, but diminished throughout, posteriorly. There was no succussion splash or shifting dullness, metallic tinkle or coin sound. There were no râles.

His teeth and gums were in good condition. The pharynx was injected. The right naris showed slight hypertrophy of the middle turbinate and slight deviation of the septum to this side. The left middle turbinate was moderately hypertrophied. He had no sense of smell. In the larynx the true cords were uniformly pink to red in color. There was no ulceration or destruction of tissue. The changes amounted to slight catarrhal laryngitis.

The apex beat was in the fifth interspace, 7 cm. from the midsternal line. The organ as a whole was slightly displaced to the right. The pulse was regular in force and tension, but of small volume. The blood pressure was systolic, 100; diastolic, 68. Physical examination was otherwise negative.

Fluoroscopic examination revealed the left lung to be about 50 per cent collapsed and there was a very small amount of fluid in the costophrenic sulcus. The heart and mediastinum were slightly displaced to the right, particularly on expiration. There was no evidence of gross parenchymal lung changes.

Stereoscopic roentgen ray films of the chest showed in the right lung that the markings throughout were intensified; the descending trunks were heavily studded; the mediastinum and heart were slightly deviated to this side. On the left side there was a hydropneumothorax with a very small

amount of fluid in the costophrenic sulcus; the lung was about 50 per cent collapsed, free of adhesions, and there was no evidence of cavity or gross pathology in it.

He had 20 cc. of muco-purulent sputum in 24 hours. Tubercle bacilli could not be demonstrated in it either on direct smear or after digestion and concentration. Seven cubic centimeters of digested sediment from 45 cc. of sputum were injected into a guinea pig on July 18, 1929. The animal was killed on October 22, 1929, and at the postmortem examination there was no evidence of tuberculosis. The Kahn test and tuberculosis complement fixation were negative.

The patient was kept at bed rest except for bathroom privileges. The râles audible on admission over the base of the right lung cleared up within the first 2 weeks. During sanatorium residence the temperature range was within normal limits. At each weekly fluoroscopic examination progressive reëxpansion of the lung was noticed. On August 13, 1929, the pneumothorax space was limited to the area above the second rib.

On August 16, 1929, he noticed he was unusually dyspneic and complained of a feeling of fullness in the chest. These symptoms appeared without apparent cause and he had not consciously strained or exerted himself in any way. This called for fluoroscopic examination which showed the right lung to be about 80 per cent collapsed and a small amount of fluid in the sulcus. Attention was focused on the collapse rather than the side, and it was presumed it was still the left lung that was involved. Subsequent events showed that this was probably an error, because on physical examination on August 29, 1929, signs of pneumothorax were found over the right side and the only abnormality over the left chest was exaggerated breath sounds. On fluroscopic examination a right-sided pneumothorax was demonstrated with the lung about 60 per cent collapsed and a small amount of fluid in the sulcus. Roentgen ray examination on August 30, 1929, showed a hydropneumothorax with the lung 50 per cent collapsed and apparently free of adhesions. There was a very small amount of fluid in the costophrenic sulcus. There was no significant change in the parenchyma of the partially collapsed lung and no evidence of cavity. The diaphragm was slightly depressed and the heart and mediastinum just a little displaced to the left. The left lung showed a pneumothorax with a very tiny amount of air overlying the apex. This would probably be overlooked without knowledge of the previous films. The patient was kept at strict bed rest and fluoroscoped once a week, being transported to the fluoroscope some 20 yards away from his room on a stretcher. Twenty cubic centimeters of fluid, which was practically all that was present, were aspirated from the right costophrenic sulcus. It was yellow in color and slightly purulent. Examination of smears by Ziehl-Neelson and Gram methods were negative. Cytologic examination revealed some polymorphonuclears. Culture on dextrose broth was negative after 48 hours. It was cultured on potato and potato-egg media, but negative for tubercle bacilli. On September 3, 1929, 6 cc. of the untreated fluid were inoculated into a guinea pig. The pig was killed on November 16, 1929, and at the postmortem examination there was no evidence of tuberculosis.

Reëxpansion took place gradually and on September 30, 1929, fluoroscopic and Roentgen ray examinations showed both lungs were completely reexpanded and there was no evidence of gross pathology in them. The patient was allowed to sit up and by easy steps worked up to increased exercise. At the time of his discharge on October 20, 1929, he was leading a normal life and apparently well. In response to a questionnaire, he replied on November 6, 1930, that he was in good health and working full time since leaving the sanatorium.

Comment. The absence of evidence of clinical pulmonary tuberculosis on physical and Roentgen ray examinations, together with

failure to demonstrate tubercle bacilli in the sputum or pleural fluid on smear, culture or animal inoculation, rules out tuberculosis as an etiologic factor in this case. As there was no obvious cause for the collapse it must be classified as benign or idiopathic pneumothorax.

Discussion of Literature. The etiology of spontaneous (idiopathic) pneumothorax is still very obscure. It may occur without any immediate appreciative cause or in the course of a more or less violent effort in a patient up to then apparently well. The gaseous effusion in the pleural cavity may dissipate rapidly without any complications or sequelæ or, rather exceptionally, it may provoke a slight pleural exudate (as in the author's case) which is usually absorbed. The condition, however, is not always benign when non-tuberculous; in an occasional case there may be much pain, dyspnea and syncope with a fatal termination.

Spontaneous bilateral pneumothorax is mostly a sequel of evolutive pulmonary tuberculosis. It is said that about 58 per cent of the cases are of this type. It may also be a sequel of well characterized emphysema and about 16 per cent answer to this type. Some cases apparently arise as a complication of traumatism and a few in association with cancer metastases.

Hainaux,[1] in his thesis (1913), collected 14 cases from the French and German literature of fatally terminating spontaneous bilateral pneumothorax as complications of evolutive pulmonary tuberculosis. The cases reported by Meyer,[2] Marshank,[3] Gray[4] and Bourne[5] were of this type also and terminated fatally. Hazen's[6] patient recovered.

The cases of Recamier,[7] Hayashi[8] and Massini and Schönberg[9] were complications of emphysema and ended fatally. Emerson's[10] fatal case followed asthma.

Elte,[11] Leclerc,[12] West,[13] Goodhart,[14] Hawes,[15] Mills,[16] and Atwood[17] reported cases of spontaneous bilateral pneumothorax following traumatism with recovery. Benedict[18] reported 3 cases with recovery.

The cases of Briggs,[19] Fleischmann,[20] Radek[21] and Borchard[22] were associated apparently with cancer metastases and ended fatally.

Olbrechts[23] distinguishes between simultaneous and successive spontaneous bilateral pneumothorax. By simultaneous spontaneous bilateral pneumothorax he designates an entrance of air into both pleural cavities either at the same time or into the second cavity before the pneumothorax in the first is absorbed. The first eventuality Obrechts says is extremely rare; he could find no categorical example of it reported in the literature, at least as far as concerned bilateral pneumothorax neither attributable to tuberculosis nor traumatism. By successive spontaneous pneumothorax Olbrechts indicates a spontaneous pneumothorax which occurs first on one side and then, later, the occurrence of a spontaneous pneumothorax on the other side. If the second pneumothorax occurs very

soon after the first *and while the latter is still unabsorbed*, it is a spontaneous bilateral pneumothorax. It is impossible to tell, when a patient presents himself with a bilateral pneumothorax, whether both occurred at the same moment or whether they were immediately successive. In the absence of absolute proof such a case must be considered as one of spontaneous bilateral pneumothorax. Sometimes there is an alternating recurrence of the pneumothorax in one pleural cavity or the other. Sometimes the interval between the successive appearances is very long. In Attwood's[17] case a man showed a left spontaneous pneumothorax at the age of 37 years and, 23 years later, developed a right spontaneous pneumothorax. Olbrechts mentions 2 cases, reported personally to him by colleagues Dr. Pauporté and Dr. C . . . (*sic*), in which the interval between the right and left spontaneous pneumothoraces was 3 years in each case. In both of these cases the original unilateral pneumothorax appears to have developed following a bronchopneumonia.

Simultaneous spontaneous bilateral pneumothorax is uncommon and most likely to be met with in traumatic cases. In Elte's case a young man developed a right spontaneous pneumothorax following a traumatism. Two days later he developed a left spontaneous pneumothorax. There was no evidence of tuberculosis. He made a rapid recovery. The case of LeWald[24] was of the same type, the second pneumothorax appearing 8 days following the first, which was accentuated at this time.

The great majority of cases of spontaneous bilateral pneumothorax are, however, of the successive type. Watson and Robertson's[25] 2 cases are more or less typical of this type. In the first case, that of a young man, aged 23 years, the condition was seen to be a spontaneous left pneumothorax. This was followed 6 months later by crises due sometimes to a right and sometimes to a left spontaneous pneumothorax. This condition of alternating left and right pneumothorax continued for some years with an apparent recovery. There was neither clinical nor radiologic evidence of tuberculosis. In the second case a young man developed symptoms of right pain and dyspnea. Radiography showed a total right spontaneous pneumothorax. A month later radiography disclosed a partial left pneumothorax. There was no evidence of tuberculosis. Grashey's[26] case was much the same.

Most of the traumatic cases are of the same kind. In Leclerc's[12] case a young man developed a left pneumothorax 3 weeks after a traumatism. A right pneumothorax developed 2 months later. The man made a rapid recovery.

Wilson[27] reported a case of successive spontaneous bilateral pneumothorax with a month's interval between the pneumothoraces on the two sides. There was no evidence of tuberculosis. The man recovered.

A few very unusual cases should be mentioned. In Bourne's[5] case the patient was an infant. Bilateral pneumothorax was found

at autopsy resulting from a miliary tuberculosis. In Scheltema's[28] case the patient was a child, aged 7 weeks, who, since birth, showed respiratory difficulty. Examination showed congenital deformities of the left hemithorax; heart displaced to the right; left diaphragm depressed, and bilateral pneumothorax. The condition suggested agenesia or aplasia of the lungs.

Little need be said regarding the etiology of spontaneous bilateral pneumothorax, as there is no definite agreement concerning it. Many consider that the rupture of a superficial tubercle is the cause of the lung rupture, but the absence of evidence of clinical tuberculosis and the significant fact that in the literature there has been no case recorded of this type in which pulmonary tuberculosis subsequently developed, is strong evidence against this view. In our own case the history of repeated colds and chest pains suggests the probability of a bilateral localized emphysema, although it could not be demonstrated clinically.

LeWald has advanced the theory that bilateralism of pneumothorax may occur from the passage of air from the right to the left pleural cavity across an orifice of the mediastinum. Fistulization of the mediastinum in the course of therapeutic pneumothorax has been reported and perforation of the mediastinum may probably occur when tuberculous ulcerations exist, but outside of such cases it seems hard to believe that LeWald's suggestion could be substantiated, more especially in nontuberculous cases. Bedford and Joules[29] reported a nontuberculous case (much like my own, except that there was no history whatever of any preceding disease) with recovery. They also suggest the possibility of leakage through the mediastinum or possibly some communication between the two pleural cavities.

The same may be said in regard to the theory of vicarious emphysema put forward by Elte.

Olbrechts thinks that it is more logical to admit that the bilateral pleuropulmonary rupture, when it is not the result of a simple coincidence, depends upon an anatomic disposition either congenital or acquired, which entrains a more or less marked fragility to the surface of the lungs.

Consideration of the literature suggests that cases of spontaneous bilateral pneumothorax associated with pulmonary tuberculosis usually end fatally. The association with emphysema or asthma is not necessary fatal and some of these patients recovery. Patients developing bilateral pneumothorax following traumatism and the so-called idiopathic cases usually completely recover. In general, the prognosis is favorable in nontuberculous spontaneous bilateral pneumothorax. In Meyer's patient spontaneous collapse took place on four occasions, each following the exertion of the coitus and the last one proved fatal.

Conclusion. A case of benign or idiopathic bilateral pneumothorax with recovery is reported, the rupture of the second lung

FIG. 1.—July 23, 1929. Spontaneous pneumothorax on the left with a small amount of fluid in the costophrenic sulcus. Right lung clear.

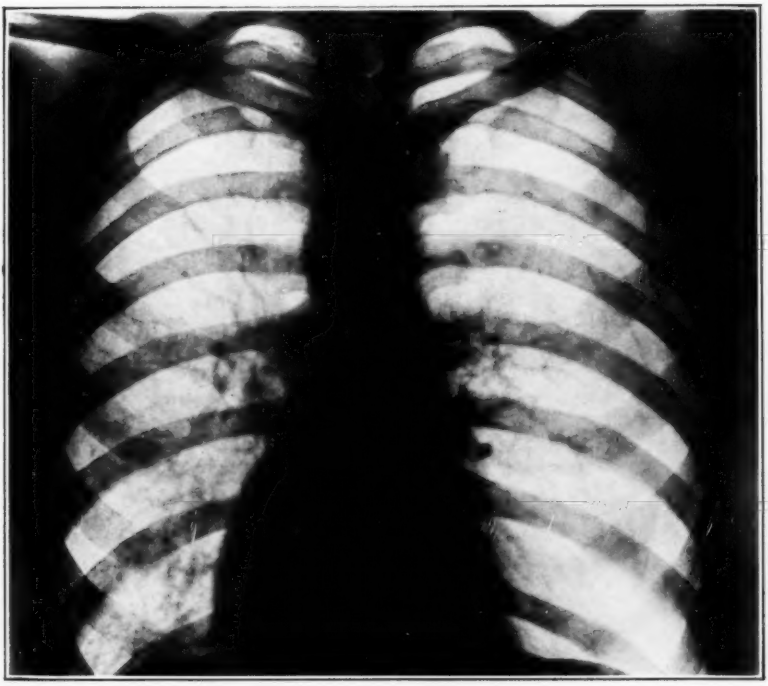

FIG. 2.—August 30, 1929. Spontaneous pneumothorax on the right side with fluid in the costophrenic sulcus. Reëxpansion of the left lung is incomplete.

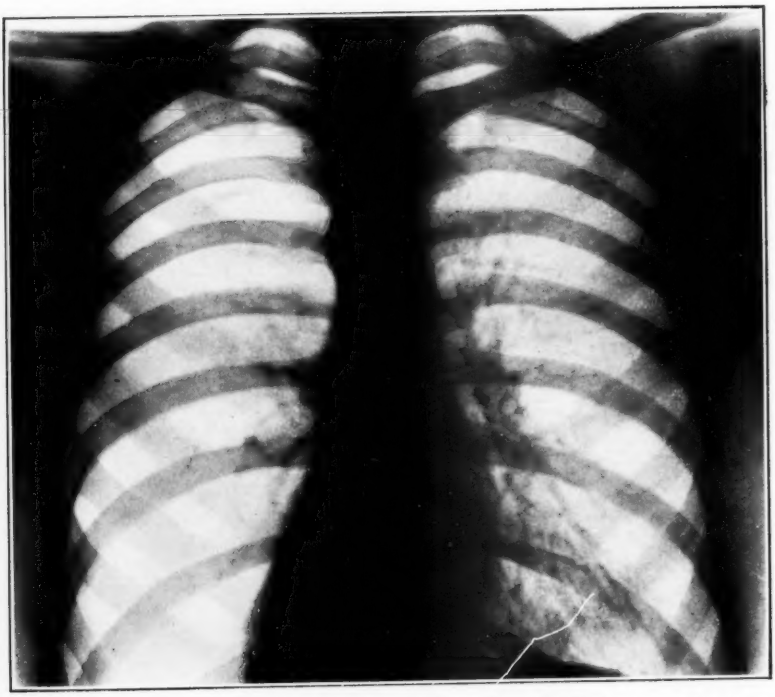

FIG. 3.—September 30, 1929. Both lungs fully reëxpanded and apparently clear.

taking place before the complete reëxpansion of the first so affected. The case may, therefore, be classed as simultaneous spontaneous bilateral pneumothorax according to Olbrechts' classification.

The literature of the subject is reviewed.

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RESPIRATORY MEASUREMENTS AS AFFECTED BY SMOKING AND BY ATHLETICS.

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Despite the widespread use of tobacco there is very little accurate information concerning its effects on the human organism. The pharmacologic actions of nicotine are well known but data as to whether chronic smoking changes the functions of the smoker are extremely few. There is no doubt that a person who is unaccustomed to tobacco may suffer unpleasant effects from his first indulgence. Certain authors (Dixon[1]) state that smoking may cause hyperacidity, and others believe this habit to be an important predisposing cause of peptic ulcer (Moynihan,[2] Harris.[3]) Other writers stress the importance of tobacco as a cause of palpitation and cardiac arrhythmias (Williamson,[4] Poulsen,[5] Sollman,[6] Dixon[1].) Tobacco has been stated to be a cause of angina pectoris. Moschcowitz[7] has reported 4 cases in which it seemed likely that such was the case. On the other hand Johnson,[8] who studied a fairly large series of cases, stated: "It is doubtful whether tobacco plays a major rôle in the etiology of angina pectoris." Johnson failed to note any difference in the blood pressure of smokers and abstainers. He believed that the chief effect of smoking was local, on the pharynx.

There seems to be a general impression that smoking "hurts the wind." Most athletic coaches and trainers forbid tobacco. So far as we know, comparative observations on the ventilation of smokers and abstainers have not been made. We have undertaken such studies with the idea of determining whether persons who smoke excessively are more short-winded than individuals who do not smoke.

Method. In a previous publication[9] a method of expressing dyspnea quantitatively has been described. This method depended on the general principle that an individual begins to feel short of breath when his actual ventilation becomes more than a certain fraction of his maximum ventilation. (In subjects with respiratory obstruction this principle is not valid.) The actual ventilation can be readily measured and the maximum ventilation in any given time is obviously proportional to the maximum ventilation for one breath, or in other words, to the vital capacity. In accordance with this principle it was shown in a series of measurements on normal subjects and on patients during various degrees of exertion, that the

degree of respiratory distress was proportional to the expression $\frac{\text{ventilation}}{\text{vital capacity.}}$ It was shown also that obese individuals had higher and thin subjects lower values for this quotient than did individuals of average nutritional state. In order to "correct" the values for such variations in weight it was necessary to have a "weight factor." It was shown by studies on groups of normal individuals of different physical makeup that the following formula was adequate for this purpose:

$$\frac{\text{Ventilation}}{\text{Vital capacity}} \times \frac{1 + \frac{\text{Ideal weight}}{\text{Actual weight}}}{2}$$

For the sake of simplicity the value arrived at by the above formula was called the Ventilation Index.

The exercise consisted of walking up, across and down from a platform 2 steps high at a given rate of speed for 2 minutes, the expired air being collected during the time and during the subsequent 5 minutes. In the original study observations were made on the ventilation during and after 4 different degrees of exertion, these consisting respectively of 6 (Exercise I), 12 (Exercise II), 16 (Exercise III) and 24 (Exercise IV) "round trips" in the 2-minute exercise. In the present study observations were made only of the second and fourth of these exercises, the former rather mild and about equal to walking at an ordinary pace, the latter being approximately equivalent to a slow run. Further details of the method are given in the paper[9] to which reference has been made.

It is evident from this description that the values for the ventilation index are entirely arbitrary in the sense that a selected exercise is performed for a given time.

The subjects studied consisted of 75 healthy medical students. Forty-two of them did not smoke. The other 33 subjects were heavy smokers in that they all smoked 20 or more cigarettes daily. Observations on occasional and moderate smokers were not made as it was felt that such studies would be difficult of interpretation.

It soon became apparent that the degree of muscular training and the individual's status as an athlete or sedentary person made a marked difference in the results. Consequently, the 2 main groups, smokers and abstainers, were subdivided into sedentary, moderately athletic and very athletic subjects. Such a classification could at best be very rough. The criteria selected were as follows: An individual who had never attempted to "make a varsity team" and who took no regular exercise was classified as sedentary. Subjects who had played on a varsity athletic team and who had continued to take fairly regular exercise in some form were classified as very athletic. Individuals whose athletic activities had been intermediate between those of these groups were considered as "moderately" athletic.

Furthermore, in order to obtain observations in a group of subjects in active "training," measurements were made on 13 members of the football squad of Vanderbilt University. These measurements were made during the football season when the men were in their best possible physical condition.

Results. A. *Comparison of the results in smokers and abstainers.* The 33 subjects who smoked were divided as follows: sedentary, 18; moderately athletic, 11 and very athletic, 4. The 42 individuals who did not smoke included 23 sedentary persons, 14 moderately athletic subjects and 5 very athletic students. Therefore, the 2 main groups—smokers and nonsmokers—were quite comparable as regards the distribution of the sub-groups.

It should be noted that the term "sedentary" as applied to the least athletic of the medical students is used in a purely relative sense. As compared to the average adult they would have to be considered as moderately athletic. Thus even the sedentary students were definitely superior in respiratory measurements to the group of normals studied by Harrison, Turley, Calhoun and Jones.[9]

The average height of the smokers was 68.4 inches; of the abstainers 69.3 inches. The average weights were 150.6 pounds and 149.6 pounds, respectively. It is evident therefore that the abstainers were, as a group, slightly taller and somewhat thinner than the smokers, although the difference was not striking. Average surface area was 1.81 and 1.82 for the 2 groups.

The respiratory measurements are given in Table 1. The average vital capacity was 2.67 liters per square meter in the smokers and 2.64 liters per square meter in the abstainers. Lowest and highest vital capacities were 1.94 and 3.37 for the smokers and 2.08 and 3.20 for the nonsmokers. It seems evident from these data that smoking has no effect on the vital capacity.

The average ventilation per square meter of the smokers was 43.3 and 70.6 for the milder and severer exercises. The corresponding values for the abstainers were 42.0 and 67.4 liters, respectively. In view of the very wide differences within a single group (Table 1) these small differences in the average cannot be regarded as significant.

Values for the ventilation index were also almost the same in the 2 groups. Averages were, for the smokers, 16.9 for the milder exercise and 27.4 for the severer exertion. The corresponding figures for the abstainers were 16.7 and 26.8. Again, the slight difference is in favor of the abstainers, but again, the differences are too small to be significant.

B. *Comparison of the results in sedentary and in athletic individuals.* Comparison of the various sub-groups in Table 1 shows that athletic individuals tend, as would be expected, to have a higher vital capacity, a lower ventilation per square meter for a given exercise, and a

TABLE 1.—SUMMARY OF RESPIRATORY MEASUREMENTS IN MEDICAL STUDENTS.

TABLE 1.—SUMMARY OF RESPIRATORY MEASUREMENTS IN MEDICAL STUDENTS.

Groups.	Number subjects.	Vital capacity, liters per square meter.		Mild exercise.				Moderately severe exercise.			
				Ventilation, liters per square meter.		Ventilation index.		Ventilation, liters per square meter.		Ventilation index.	
		Range.	Average.	Range.	Average.	Range.	Average.	Range.	Average.	Range.	Average.
Smokers:											
Sedentary . .	18	1.99–3.33	2.63	34.0–51.6	43.5	12.8–22.6	17.3	59.6–86.7	73.1	21.1–41.1	29.2
Abstainers:											
Sedentary . .	23	2.08–3.20	2.62	33.0–48.7	42.7	11.4–23.3	17.6	55.0–87.4	70.0	23.1–35.7	28.4
Smokers:											
Moderately athletic . . .	11	2.40–34.9	2.70	35.8–50.2	43.6	13.2–22.1	17.0	41.4–87.9	68.1	19.4–32.7	26.3
Abstainers:											
Moderately athletic . . .	14	2.41–2.87	2.62	34.7–47.6	41.4	12.0–20.5	16.5	49.3–82.0	65.2	21.1–30.6	25.9
Smokers:											
Very athletic .	4	2.50–3.37	2.90	39.5–44.5	42.9	12.2–16.4	14.9	55.4–77.4	66.9	17.2–27.6	23.4
Abstainers:											
Very athletic .	5	2.60–2.98	2.83	29.9–45.9	40.4	9.9–16.3	14.5	58.6–62.8	61.1	20.3–22.7	21.8
Smokers:											
Entire group .	33	1.99–3.49	2.67	34.0–51.6	43.4	12.2–22.6	16.9	41.4–87.9	70.6	17.2–41.1	27.4
Abstainers:											
Entire group .	42	2.08–3.20	2.64	29.9–48.7	42.0	9.9–23.3	16.7	49.3–87.4	67.4	20.3–35.7	26.8

TABLE 2.—COMPARISON OF RESPIRATORY MEASUREMENTS IN FOOTBALL PLAYERS WITH THOSE IN SEDENTARY MEDICAL STUDENTS.

Groups.	Number subjects.	Vital capacity, liters per square meter.		Mild exercise.				Moderately severe exercise.			
				Ventilation, liters per square meter.		Ventilation index.		Ventilation, liters per square meter.		Ventilation index.	
		Range.	Average.	Range.	Average.	Range.	Average.	Range.	Average.	Range.	Average.
Football players .	13	2.24–3.58	2.76	40.5–50.7	45.4	12.8–19.0	16.4	48.8–83.3	66.1	19.9–31.0	23.7
Sedentary medical students . . .	41	1.99–3.33	2.62	34.0–51.6	43.1	11.4–23.3	17.3	55.0–87.4	71.5	21.1–41.1	28.8

lower ventilation index than do sedentary individuals. The differences in favor of athletes are scarcely large enough to be significant for the mild exercise but are more pronounced for the severer exercise.

The average values for 13 members of the Vanderbilt University football team are shown in Table 2. For the sake of comparison the average values for the sedentary individuals (both smokers and abstainers) of Table 1, are also included. It can be seen that the average vital capacity of the football players was only about 5 per cent greater than that of the sedentary students. For the milder exercise the football players had slightly greater ventilation per unit of body surface than did the nonathletic controls. For the severe exercise the ventilation was considerably (about 8 per cent) less than that of the sedentary individuals. The ventilation index of the athletes was about 5 per cent lower for the milder exertion and about 20 per cent lower for the severer exercise than were the corresponding values for the sedentary students. It is evident that individuals in good "training" breathe considerably more efficiently with unusual exertion than do untrained subjects but that they are not much more efficient in the performance of mild exertion.

A comparison was made between the value to the team of the different football players with the respiratory measurements but it was soon seen that no correlation existed. Two of the players with the highest (poorest) ventilation indices were "stars" and several individuals with the lowest (best) ventilation indices were "scrubs." It is evident that in a group of individuals, all of whom have an excellent physique, the "stars" are not necessarily the men with the best "wind."

The "very athletic" medical students, who were all in excellent physical condition and all of whom took regular exercise, but none of whom were highly trained in the same sense that the football players were, had according to the respiratory measurements, just as good "wind" as did the football players. This finding was rather surprising. Possibly, the latter group would have been superior had the subjects been tested with violent or maximal exertion.

Discussion.—From the above data one might be tempted to conclude that smoking does not affect the "wind" at all. However, such a conclusion seems to us to be unjustifiable for the following reasons:

1. The subjects, being young, had been smoking for relatively few years. It is conceivable that studies on a group of individuals who had been heavy smokers for 20 or more years might show difference from a control group.

2. It is also possible that if a maximal or violent test exercise had been used the smokers would have shown themselves less efficient than the abstainers.

The data do seem to justify the following conclusion: Smoking

for a few years, even to excess, produces no significant decrease in the respiratory efficiency in response to such exertion as is necessitated by the ordinary duties of life.

The data concerning athletes were of interest. For mild exercise the athletes were only slightly more efficient than the sedentary students, but for severe exercise which was in no sense maximal, the football players were about 20 per cent more efficient than the sedentary students. Of special interest is the fact that those medical students who had participated in intercollegiate sports some years before and who had continued to take some form of regular exercise, but who were not in active training at the time the tests were made, were just as efficient in their breathing as were the football players who were highly trained at the time the tests were made.

It appears that once an excellent physical status has been attained, one is able to keep in this condition, for a number of years at least, by relatively mild exercise if it be taken regularly.

Summary. Respiratory measurements were made on a group of 75 medical students and on 13 football players in active training. As a result of these measurements the following conclusions were drawn:

1. "Heavy" smoking (20 or more cigarettes a day) for several years does not significantly diminish the respiratory efficiency in the performance of mild and moderately severe exercise.

2. Athletic individuals are not much more efficient than sedentary persons in the performance of mild exertion, but are considerably more efficient in carrying out moderately severe exercise.

3. Individuals who have once been highly trained, remain extremely efficient in their breathing for a number of years after giving up active training, provided they take fairly regular exercise.

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REVIEWS.

A Radiological Study of the Paranasal Sinuses and Mastoids. By Amédée Granger, K.C.B., K.C.I., M.D., F.A.C.R., Professor of Radiology, Louisiana State University Medical Center, and Director of the Department of Radiology, Louisiana State Charity Hospital, New Orleans. Pp. 186; 113 illustrations. Philadelphia: Lea & Febiger, 1932. Price, $5.50.

The otolaryngologist who is not satisfied with his knowledge of sinus films will do well to read the text of this book and study the plates presented. By so doing his information concerning the correct interpretation of sinus roentgenograms will be greatly increased. In addition he will learn if his roentgenologist is securing the detail which Granger demonstrates. This is especially true of the sphenoid air spaces concerning which Roentgen ray information is not infrequently unsatisfactory. The plates of illustrative cases demonstrate the author's points very clearly. In lesser degree the same may be said of the mastoid presentation. Unfortunately the illustrative mastoid films do not always give the detail called for in the author's text.

K. H.

Clinical Roentgen Pathology of Thoracic Lesions. By William H. Meyer, M.D., Professor of Roentgenology in the New York Post-Graduate Medical School of Columbia University, etc. Pp. 272; 183 engravings. Philadelphia: Lea & Febiger, 1932. Price, $6.00.

The author has presented in a very concise and unique manner a book on diseases of the thorax and its contents. I presume that this book was prepared particularly for matriculates of his school. It contains detailed systematic plans for the examination of the chest, and anyone who follows such a plan would be prevented from overlooking most lesions. The author has considered technique, pathology and most of the adjuncts that radiologists use in determining the nature of the lesion which they are studying.

The discussion of the diseases with their roentgenographic manifestations is very concise. In fact, one obtains the impression that it is too concise in some instances; but at least it does give the student the usual textbook appearance of certain conditions, and if he is interested he will look elsewhere for additional data. The book contains no bibliography but the Reviewer gains the impres-

sion that the author has searched rather widely for his material, and this combined with his own large experience makes the book worth while.

The illustrations are very good, especially when one considers that they are all negatives. The pencil drawings greatly aid in the interpretation of the lesions. Unfortunately, the illustrations are not uniform. Namely, the heart is at times on one side, and then on the other. This makes it difficult to interpret when the legend and the side on the illustration do not correspond. The print is readable and the subjects are set apart throughout the entire book. The paper is glossy, which makes it a little more difficult to read.

E. P.

NERVOUS INDIGESTION. By WALTER C. ALVAREZ, M.D. Pp. 297. New York: Paul B. Hoeber, Inc., 1930. Price, $3.75.

IN this volume the scientist or intelligent physician will find little of interest. From the standpoint of sound, physiological data on the question of nervous influences on the gastrointestinal tract this book offers nothing that cannot be found in much greater detail, and in far more satisfactory manner in "The Mechanics of the Digestive Tract" by the same author. Even the sketchy material offered on this question loses considerably in value because of the lack of an adequate bibliography. It is true that the author tells many interesting anecdotes about people with nervous disorders of the digestive tract. Yet, even in this regard, it would be a safe venture that the average practitioner from coast to coast could ably swap stories about neurotics with Dr. Alvarez for hours without feeling in the least a sense of inferiority. It is the avowed purpose of the book to focus the attention of students of medicine, and of general practitioners, on the importance of functional disorders of the digestive tract. The degree to which this is accomplished must be judged by each individual reader.

M. F.

THE DIAGNOSIS AND TREATMENT OF VENEREAL DISEASES IN GENERAL PRACTICE. By L. W. HARRISON, D.S.O., M.B., CH.B., F.R.C.P.E., Brevet Colonel, R.A.M.C., and K.H.P. (RET.), Director of Venereal Department, St. Thomas's Hospital. With a chapter on The Medico-Legal Aspects, etc., by F. G. CROOKSHANK, M.D., F.R.C.P., etc. Pp. 567; 79 illustrations. Fourth edition. New York: Oxford University Press, 1931.

THIS book, the fourth, enlarged edition of a well-known text, presents the views of one of the best known and highly organized

venereal disease services in the world, that of Great Britain, and is an exceptionally concise and trustworthy manual for the general practitioner. Condensation of material adds to its practical value as a small but authoritative volume in which the author shows an extraordinary acquaintance with the literature of his subject.

The regional presentation of material and the attempt to interweave the manifestations of syphilis and gonorrhea, while of some service to the practitioner, probably makes less appeal to the specialist in urology or syphilology as such.

The frankness of the chapter dealing with the prevention of venereal diseases is a welcome relief from the usual prudery that envelops these issues. J. S.

NOSOKOMEION, QUARTERLY HOSPITAL REVIEW. First special number, containing the reports presented to the Vienna Congress. Pp. 492. Stuttgart: V. W. Kohlhammer, 1931. Price, 15 marks.

THE first special issue of *Nosokomeion*, a quarterly hospital review, published by V. W. Kohlhammer, Stuttgart, presents the reports of the second International Hospital Congress held in Vienna, June 8 to 14, 1931. This volume consisting of 492 pages is printed in German, French and English, although French is the official language of the Congress. The advantage to the hospital world generally of this triple language presentation is evident since the vast majority at least of administrators of American hospitals are not sufficiently acquainted with German and French to enable them to secure the greatest benefit from a volume not so printed.

Few realized in 1927 the far-reaching effect of a preliminary meeting held in the Red Cross Headquarters in Paris, France, at which 14 countries were represented. The writer of this review, being present on this occasion, noted the very marked interest displayed in the formation of an International Hospital Congress by those present. The first meeting of this Congress in Atlantic City in 1929 brought forth some splendid contributions to the hospital literature and attracted the attendance of the representatives of over two score countries. The Vienna Congress, at which delegates from almost every government of size in the world were in attendance, apparently exceeded in size and literary contribution the Atlantic City meeting.

The program consisted of the discussion of 10 major subjects, including construction, nursing, medical services, physiotherapy, occupational therapy and social service. A splendid address was delivered by Prof. Dr. Julius Tandler, Director of Vienna Public Health and Social Welfare Services, who is the president of the organizing committee, opened the Congress.

Dr. René Sand, of the Red Cross Society, who acted as the official

host in the name of the Red Cross to the organizing committee, and who served most effectively as interpreter, reviews in this volume the development of the International Hospital movement.

One of the outstanding contributions was that included in a report of the Committee on Nursing, headed by Miss Christine Reimann, chairman of this committee, and a representative of the the International Nursing Association on the Ratio of Nurses to Patients. This committee exhaustibly discusses the nursing situation throughout 22 countries. One is struck with the great variance in patients per nurse, in working hours, in annual vacation and in working conditions under which nurses labor throughout the world. There still exist in many countries relics of the pre-Nightingale era in regard to requiring too long tours of duty and of exacting from nurses, drudgery which appears both unfair to the nurses and economically expensive to the hospital. More than that, this committee demonstrates that where too long working hours are found and where the labors of the nurse are physically too exacting, the average number of days lost yearly for sickness rises rapidly. Thus it amounts from 4.1 for the trained nurse and 5.9 for the student nurse in the United States, to 16.8 and 14.9 respectively in Austria. In scanning the report of the conditions under which nurses work throughout the world, one cannot help but conclude that the nursing situation here in the United States ranks rather high, notwithstanding the unfavorable comment which one hears so frequently.

A splendid discussion by Dr. Wirth, of Frankfurt, urges on The Unification of Hospital Nomenclature. This matter should interest not only governmental and private statistical agencies, but all hospitals throughout the world. The classification of diseases and causes of death certainly requires some attempt at standardization.

What Dr. Alter, of Düsseldorf, has termed "the third indispensable service" of the hospital, *i. e.*, the care of the soul through occupational therapy, social service and other humanitarian activities, is discussed by Dr. Wortman, of Hilversum, Netherlands. Professor von Noorden, of Vienna, presents in this volume a splendid article on "Nutritional Service in the Hospital." Dr. Alter, of Düsseldorf, discusses the place of neurology and psychiatry in the general hospital. Dr. Layton, of London, presents a report outlining the advantages which public health derives from the coöperation of social insurance in the hospital. Dr. Corwin, of New York, presents the problem of the development and integration of dispensaries in and with the hospital.

Not only to hospital administrators is this number of *Nosokomeion* of great interest, but it contains much useful information which should appeal to physicians, sociologists and all others interested in community health. J. D.

CLINICAL DIETETICS. By HARRY GAUSS, M.S., M.D., F.A.C.P., Instructor in Medicine, University of Colorado, School of Medicine, Assisted by E. V. GAUSS, B.A., formerly Assistant Dietitian, Presbyterian Hospital, Denver, Colo. Pp. 490; 59 illustrations. St. Louis: The C. V. Mosby Company, 1931. Price, $8.00.

THE outgrowth of a course of lectures on the subject given by the senior author in the medical school of the University of Colorado, the book is a clear, concise, orderly presentation of the subject. Lacking the great detail of the usual more extensive works on dietetics, it nevertheless gives the practical essentials. This fact, together with the numerous specimen diets worked out on a weekly program basis, should make it very useful to practitioners. There are few criticisms: pernicious anemia is attributed to a simple avitaminosis, an unwarranted assumption. There is no mention of the possible use of high protein diets in nephrosis. It is fallacious to assume that a patient who has been put on the 5 elimination diets noted and has not been made free of symptoms is not troubled with food allergy—it merely proves that he is sensitive to more than a single food. Finally, there is no bread but whole wheat in the authors' opinion, but then every dietitian rides a hobby.

R. K.

COSMIC CONSCIOUSNESS. By RICHARD MAURICE BUCKE, M.D., Formerly Medical Superintendent of the Asylum for the Insane, London, Canada. Pp. 384; 1 illustration. New York: E. P. Dutton & Co., Inc., 1931. Price, $5.00.

BY "Cosmic Consciousness" the author signifies a form higher than either the self-consciousness possessed by the ordinary man or the simple consciousness of animals. Concerned with the life and order of the whole universe, this form of intellectual enlightenment is looked upon as a state of moral exaltation which has been experienced by a relatively few individuals, but in increasing numbers as civilization progresses. The major part of the book describes 14 instances of "Cosmic Consciousness," from Gautama the Buddha to Edward Carpenter, with 36 lesser or doubtful instances.

The bibliographic history of this book is unusual. Passing through 3 small editions between 1901 and 1912, it was practically lost for 10 years, after which Dutton has published 4 editions in the past eight. To the Reviewer the book proved but mildly interesting and still less enlightening, with a tiresome mysticism and frequent unjustifiable deductions. Nevertheless William James considered it "an addition to psychology of first rate importance" and the cover carries equally favorable comments. Let each reader decide for himself.

E. K.

A HISTORY OF SCIENCE. By WILLIAM CECIL DAMPIER DAMPIER-WHETHAM, M.A., F.R.S., Fellow and sometime Senior Tutor of Trinity College, Cambridge; Fellow of Winchester College. Pp. 514; 14 figures. New York: The Macmillan Company, 1931. Price, $4.00.

ALTHOUGH it has been rather generally accepted that the scientists, artists and artisans of modern times have done far more to benefit the human race than have rulers, statesmen and warriors, still it is the history of the latter group that is best known and most carefully studied. Only in the past two decades has an increasing interest in the History of Science been apparent, as manifested by the growing list of recent books on the subject, by the Journal "Isis," by works like Sarton's splendid first volumes of an Introduction to the History of Science and by the various national and international societies interested in the subject.

The demand within a year for another edition of this thoughtful book by Dampier-Whetham is another encouraging example of recent trends and shows the interest created by such works in the minds of a wider circle than those of professional scientists. And such popularity has in no sense been obtained by sacrifices to a popular style. Scholarly but readable, it accomplishes in 10 chapters an account of science from the dawn of civilization down to its most recent developments. The "New Era in Physics," for instance, devotes 63 pages to radio-activity, quantum mechanics, relativity and the other surprising developments of the past 40 years, Nor are philosophic applications shirked; in the last chapter especially, "Scientific Philosophy and Its Outlook," mathematics, logic and metaphysics are frankly applied to such concepts as determinism and religion with the resultant confessions of ignorance now so popular among physicists. "But, now or later, intelligible mechanism will fail, and we shall be left face to face with the awful mystery which is reality." "*Credo quia impossible,*" said Tertullian. E. K.

FIGHTING DISEASE WITH DRUGS. Edited by JOHN C. KRANTZ, JR., with an introduction by Dr. JAMES H. BEAL. A publication of The National Conference of Pharmaceutical Research. Pp. 230; 27 illustrations. Baltimore: Williams & Wilkins Company, 1931. Price, $2.00.

THIS is a symposium containing 12 chapters, each written by a specialist, dealing with the history of pharmacy, the sources, chemistry, and standardization of drugs and the relation of modern pharmacy to the community and to science in general. It is written for the average layman, for the purpose of acquainting him with the

part played by pharmacists and pharmacy in the development of modern therapeutics. Such a reader will be left with a higher opinion of the practitioner of pharmacy than he had before, and with a good idea of the problems which have been solved and which await solution in the development of chemical and biologic remedies. For the physician, the chapters on Dawn of Pharmacy (Dohme), Bacteria-made Drugs and Vitamins (Anderson) and Drugs Made by Man (Adams and Kamm) contain much of interest.

C. S.

BOOKS RECEIVED.

NEW BOOKS.

The Practice of Contraception. Edited by MARGARET SANGER and HANNAH M. STONE, M.D. With a Foreword by ROBERT L. DICKINSON, M.D. Pp. 316; 22 illustrations. Baltimore: The Williams & Wilkins Company, 1931. Price, $4.00.

Neoplasms of Domesticated Animals. (Mayo Clinic Monograph.) By WILLIAM H. FELDMAN, D.V.M., M.S., Division of Experimental Surgery and Pathology, The Mayo Foundation. With a Foreword by CHARLES H. MAYO, M.D. Pp. 410; 193 illustrations. Philadelphia: W. B. Saunders Company, 1932. Price, $6.00.

Gynecological Roentgenology. By JULIUS JARCHO, M.D., F.A.C.S., Attending Gynecologist and Obstetrician, Sydenham Hospital, New York. Vol. 13 of Annals of Roentgenology. Edited by JAMES T. CASE, M.D., Professor of Roentgenology, Northwestern University Medical College, Chicago. Pp. 571; 273 illustrations, 5 colored plates. New York: Paul B. Hoeber, Inc., 1931. Price, $20.00.

Experimental Researches on Precancerous Changes in the Skin and Skin Cancer. By GUSTAV GULDBERG. Pp. 223; 26 illustrations. Copenhagen: Levin & Munksgaard, 1931.

The Harvey Lectures, 1930–31, Series 26. Pp. 186; illustrated. Baltimore: The Williams & Wilkins Company, 1931. Price, $4.00.

Acta Societatis Medicorum Fennicae. Edited by S. E. WICHMANN, Professor Ord. Universitatis. *"Duodecim," Series B., Vol. XV.* Pp. 546; illustrated. *"Duodecim" Series B, Vol. XVI.* Pp. 695; illustrated with charts and tables. Helsinki, 1931.

The White House Conference Publications on Child Health and Protection. New York: The Century Company, 1932. *I. Health Protection for the Preschool Child.* By GEORGE TRUMAN PALMER, DR. P. H., Chairman, Subcommittee on Statistics, MAHEW DERRYBERRY, Research Assistant and PHILIP VAN INGEN, M.D., Chairman, Committee on Medical Care for Children. Pp. 275; 50 charts and numerous tables. (1931.) Price, $2.50. *II. Body Mechanics: Education and Practice.* Report of the Subcommittee on Orthopedics and Body Mechanics, ROBERT B. OSGOOD, M.D., Chairman. Pp. 166; illustrated. Price, $1.50. *III. Psychology and Psychiatry in Pediatrics: The Problem.* Report of the Subcommittee on Psychology and Psychiatry, BRONSON CROTHERS, M.D., Chairman. Pp. 146. Price, $1.50.

PROGRESS
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MEDICINE

UNDER THE CHARGE OF

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Histologic Studies of the Bone Marrow in Fasted and Polyneuritic Pigeons.—Of increasing interest is the attention that is being paid to anemias which develop as a result of certain nutritional deficiencies. MOORE and BARLOW (*J. Exper. Med.*, 1931, **54**, 761) have investigated the bone marrow in pigeons fed upon a diet of rice contrasted with a group which were fasted. The conclusions drawn by the authors are to the effect that the changes in the bone marrow in the fasted and rice-diseased pigeons are essentially the same. In pure vitamin B deficiency there is degeneration and edema and slight endothelial proliferation of the small vascular channels but with active hematopoiesis. The anemia of rice disease in pigeons is apparently not particularly related to vitamin B deficiency but depends upon the starvation anemia.

Reticulocyte Response to Glutamic Acid in Pernicious Anemia.—The use of glutamic acid as an antianemic substance was suggested to LICHTMAN (*Proc. Soc. Exper. Biol. and Med.*, 1931, **29**, 153) by the fact that the acid may be condensed into pyrrolidonecarboxylic acid, which is one of the isolated substances in the liver tissue identified by West, Howe and Dakin as pyrrole precursors active in Addisonian anemia. Furthermore, several other authors have found the acid and certain other amino acids are effective in the treatment of the anemia of rats who are fed on an exclusive milk diet. These particular pyrrole substances, it is suggested, are probably liberated from certain protein foods through the action of normal gastric digestion and are then decomposed so that their products after absorption are capable of playing a part in the synthesis of hemoglobin and erythrocyte stroma. In pernicious anemia the necessary substances are not available to the organisms due to some deficiency of the gastrointestinal tract. Lichtman therefore fed glutamic acid to 4 patients with pernicious anemia. A condiment, Suzuki, exceedingly popular in Japan which contains

sodium-glutamate was the form in which the glutamic acid was administered. He found that there was some slight reticulocyte response in the 4 patients studied, the maximum response being 6 per cent. There was no rise in the hemoglobin or erythrocyte count except in 1 patient in which the hemoglobin went up but the red cells were not increased. The conclusion is drawn that sodium glutamate, while not completely devoid of activity as shown by definite retoculocyte response in the 4 cases studied, is not however an effective substitute for liver extract in the treatment of pernicious anemia.

SURGERY

UNDER THE CHARGE OF
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The Peptic Genesis of Gastric and Duodenal Ulcer.—LUDAN and WOLFF (*Surg., Gynec. and Obst.*, 1931, **53**, 621) say that a survey of the experiences acquired will show that, in the biochemical theory, there is an exceedingly good explanation of the nature as well as the location of the peptic lesions with ulcer formation, confined to the esophagus, cardia, area of the pyloric glands, duodenum, jejunum (postoperatively) and in Meckel's diverticulum. Everywhere the lesion is to be found in the area of activity of the hydrochloric acid. The presence of free hydrochloric acid has likewise proved to be a regular finding. This biochemical theory now advanced anew and further developed by Buechner has, in fact, been taken up and confirmed by several leading investigators. Aschoff and Kolk also in recent monographs have expressed the opinion that the gastric juice has again marched to the foreground as a genetic factor of ulcer, contending however, that the excess of hydrochloric acid is due to a "Dysharmonie des Vegetativen Nervensystems." The main object would be to control and reduce as far as possible, the production of hydrochloric acid by suitable dieting in accordance with the experience gained chiefly through the Pavlov school. Considering surgical therapy with its rather varying measures, the operation, Billroth I, which reduces the production of hydrochloric acid, removes that part of the gastral system which is most susceptible to ulceration, while retaining to the greatest possible extent the normal topography and normal discharging conditions, is probably the method that yields the best results and shows extremely few or no cases of relapse or postoperative ulcer.

The Roentgen-rays and Radium in the Diagnosis and Treatment of Carcinoma of the Bladder.—PFAHLER (*Surg., Gynec. and Obst.*, 1931, **53**, 680) says that pneumocystography is a valuable means of determining the presence, size, outline, position and amount of infiltration of a carcinoma of the bladder. It can be carried out by any careful roentgenologist with sterile catheter, atomizer, bulb and a hemostatic forceps. Radiotherapy involves treatment by radium in the form of capsules, needles or seeds (glass or gold) and by the use of deep roentgenotherapy,

either alone or before or after electrocoagulation. It seems that electrocoagulation is better than excision, followed by radium or Roentgen ray treatment. Some very encouraging results have been obtained by irradiation alone. Under such treatment the patient is usually relieved of hemorrhage and pain. If results can be made permanent and percentage of cures increased, and if in the early stages the growth can be destroyed cystoscopically, it will be a great step in advance.

Paget's Disease—A Predisposing Factor to Osteogenic Sarcoma.—COLEY and SHARP (*Arch. Surg.*, 1931, **23**, 918) state that it was found from a study of cases of osteogenic sarcoma in Memorial Hospital, that in no patient was this condition associated with Paget's disease prior to the age of 50 years. In a collected series from Memorial Hospital and the Bone Registry of 71 cases of osteogenic sarcoma in patients over 50 years of age, Paget's disease was found to be a predisposing factor to osteogenic sarcoma in 28 per cent. Men are affected five times more frequently than women—among patients with the two diseases associated. In general it may be said that osteogenic sarcoma in patients over 50 has the same sites of predilection as in younger persons. A patient over 50 with osteogenic sarcoma of the skull presumably has Paget's disease. When osteogenic sarcoma is associated with Paget's disease it invariably develops in a bone showing the characteristic changes of Paget's disease rather than in an otherwise normal bone. Evidence is presented to show that Paget's disease is present from 10 to 15 years or more prior to the development of a complicating osteogenic sarcoma. The duration of life is shortened by the association of osteogenic sarcoma with Paget's disease, as determined by a comparative study of a group of patients of the same age without osteogenic sarcoma. No record has been found of the survival for 5 years of a patient with osteogenic sarcoma and Paget's disease under any method of treatment. Paget's sarcoma has proved to be relatively resistant to radiation.

Some Thoughts on the Problem of Cancer Control.—COLEY (*Am. J. Surg.*, 1931, **14**, 605) says that a considerable portion of the funds raised for cancer control should be expended in the field of collecting more facts especially more accurate first-hand information, as to the geographic distribution of cancer and especially data that may account for the wide variation in incidence. Little advance may be expected in the surgical treatment of cancer, but in the field of Roentgen ray and radium with increasing knowledge of the action of these agents and with improved technique, considerable advance may be anticipated. Radiation has already displaced surgery in certain fields, *i. e.*, cancer of the skin, of the cervix and oral cancer. It is rapidly becoming recognized that most cases of cancer can best be treated by a combination of surgery and radiation, rather than by the use of either alone. A systematic attempt should be made to give the undergraduate medical student much better clinical instruction in the early diagnosis of cancer than he has had in the past and even more important is it to provide numerous centers where intensive postgraduate instruction may be obtained. The results of study by the various organizations and individuals working on the problem of cancer, including both the clinical and laboratory aspects, should be given wide publicity.

THERAPEUTICS

UNDER THE CHARGE OF
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The Treatment of Angina Pectoris With Tissue Extract.—Following suggestive leads given by the observations of Frey and Kraut, Gley and Kisthinios, Schwartzman and others, WOLFFE, FINDLAY and DESSEN (*Ann. Inter. Med.*, 1931, **5**, 625) prepared a purified extract of pancreas according to the method of Gley and Kisthinios. They find this extract to be entirely free of histamin and virtually free of insulin. They report experiments upon animals and observations on the therapeutic effects in man. Administration of the extract to animals produces a sharp drop in blood pressure followed by fairly prolonged maintenance of the pressure at a lowered level. It also antagonizes more or less effectively the vasoconstrictor action of epinephrin. In addition it slows the heart rate. The extract does not seem to be antigenic nor does it have demonstrable toxic effects upon animals. The extract was standardized upon rabbits, one hypotensive unit being that amount which produces a just appreciable fall in blood pressure when injected intravenously into a rabbit weighing 2 kg. For clinical trial a concentrated extract was employed which contained 15 units per cc. The extract was given intramuscularly to a series of patients suffering from angina pectoris which was unrelieved or insignificantly influenced by the usual methods of treatment. The doses employed varied from 60 to 150 units, the usual dose being 75 units. No significant ill effects were observed in this group of patients and complete clinical relief of pain was secured in 55 per cent, partial relief in 30 per cent while in 15 per cent there was no benefit. One patient was relieved both of his angina and of a severe associated intermittent claudication. The authors present this early report with the belief that the extract promises to be of great value as a therapeutic agent and in the hope that it may promptly be put to sufficient controlled clinical trial to determine its value and limitations. They point out that the extract is not a hormone but that its action depends upon a vasodilator principle which is either adenylic acid or adnosine, both of which may be obtained from various body tissues.

Intravenous Quinidin Therapy.—PADILLA and COSSIO (*Arch. des Mal. du Coeur, etc.*, 1931, **24**, 401) made careful trials to determine whether or not the intravenous administration of quinidin could be carried out safely in man and found that such was the case provided that certain conditions were met. The solution should not be more concentrated than 5 per cent of quinidin in physiologic saline. The

injection should be carried out slowly. The patient should be recumbent during the injection. The single dose of quinidin should be about 0.5 gm. for the majority of cases and even in exceptional cases it should not exceed a maximum of 0.15 gm. of the sulphate for each 10 kilos of the patient's body weight. Following these established conditions, the authors administered quinidin sulphate intravenously to a series of patients without once encountering serious toxic effects. Reporting 4 cases in some detail and analyzing the previous literature they conclude that the intravenous injection of the drug is especially indicated in patients with prolonged paroxysmal tachycardia, especially where it has proved resistant to the more usual methods of treatment. Such injections of quinidin are almost invariably effective in immediately arresting the tachycardia and restoring normal rhythm. The intravenous injection of quinidin is also indicated in certain cases of auricular flutter, especially in paroxysmal types. In these conditions, however, its chief action is to diminish the ventricular rate by depressing auriculoventricular conduction. Minor toxic symptoms may appear such as occasional marked pain along the course of the injected vein which seems to depend chiefly upon a too rapid injection. With the rapid return of normal rhythm and much slower rate in cases of paroxysmal tachycardia transitory symptoms of lassitude, pallor, cold sweating and slight visual disturbances are occasionally seen. There are also occasional instances in which the patient complains of rather intense precordial oppression which may or may not be accompanied by dyspnea, profound lassitude, ringing in the ears, vertigo, nausea, vomiting, etc. These symptoms, however, are rarely either lasting or important.

The Reaction to Nitrites in Angina and Hypertension.—It is a well established fact that nitrites are capable of relieving the pain in the majority of patients with the anginal syndrome, whether this pain be associated with hypertension or not. It is further a well known fact that the nitrites generally produce a rapid but transitory fall in blood pressure. There has been considerable speculation as to the mechanism by which the nitrites accomplish the relief of anginal pain, and especially as to the relationship between this specific relief of pain and their vasodilator effects. In order to throw further light upon these problems, BURGESS (*Ann. Int. Med.*, 1931, **5**, 441) carried on a group of carefully controlled clinical investigations from which he concludes as follows: Neither nitroglycerin nor amyl nitrite produce any consistent blood pressure change other than slight transitory lowering in normal persons or in persons with simple or complicated hypertension. Although a brief reduction of pressure follows their administration in the majority of cases with angina, close study shows that the relief of pain is independent of this effect, both in point of time and in point of the extent of the lowering of pressure. It is a demonstrated fact, however, that the nitrites cause a pronounced increase in coronary blood flow which also is apparently unrelated to their action upon the systemic circulation. The author concludes from these observations that the pain of angina is probably due to a relative ischemia of the myocardium and that its relief by nitrites is due to their rapid production of increased flow through the coronaries with improved nutrition of the heart muscle.

PEDIATRICS

UNDER THE CHARGE OF
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Phosphorus Metabolism in Infants.—WITT (*Am. J. Dis. Child.*, 1932, **43**, 306) studied the phosphorus metabolism in a group of 5 apparently healthy infants, each of whom was fed breast milk and cow's milk mixtures during alternate periods. This was done to exclude variations that might arise as a result of constitutional differences in the experimental subjects. Individual 24 specimens have no value for metabolic investigations. Analysis of the average values for three consecutive 24-hour periods shows distinct differences produced by change of diet. The average intake of phosphorus with cow's milk was 0.654 gm. per 24 hours and with breast milk 0.258 gm. The total output during the periods when cow's milk was used was almost four times as great as that during the periods of breast feeding. There was an output of 0.394 gm. per 24 hours during cow's milk feedings as compared to 0.108 gm. during the periods of breast milk feeding. The increased output during the feeding of cow's milk is due to a great extent to the increased phosphorus during these periods. The average excretion of phosphorus in the urine was 0.275 gm. per 24 hours during the period of cow's milk feeding and 0.064 gm. when breast milk was fed. The average value for phosphorus excreted in the feces was 0.119 gm. per 24 hours for cow's milk and 0.044 gm. for breast milk. The actual phosphorus absorbed by the infants studied was considerably more during the periods of cow's milk feeding; the average value for cow's milk, 0.535 gm. per 24 hours, compared to 0.213 gm. for breast milk. The average percentage absorption for breast milk was 83.1 per cent as compared to 81.1 per cent for cow's milk. The actual amounts of phosphorus retained were considerably greater during the periods when cow's milk was used, possibly as the result of a greater intake, and for this reason it was difficult to compare the percentage values for retentions. Over 50 per cent of the phosphorus intake was retained by each infant during the periods when it was breast fed, and the values ranged from 51 to 63.8 per cent, with an average of 58.1 per cent. During the periods when cow's milk feedings were given the retention was always below 50 per cent, the maximum being 44.2 per cent and the minimum 29.2 per cent. The values per kilogram obtained during the periods when the baby was breast fed indicated that the optimal absorption and retention of the phosphorus in breast milk occurred in the earliest months of life.

Basal Metabolism of Normal Children—The Puberty Reaction.—POPPER and MULIER (*Am. J. Dis. Child.*, 1932, **43**, 327) studied the basal metabolism of 28 girls and 10 boys from 10 to 16 years of age at intervals of 6 months to a year above a period of from 1 to 4 years. It was found that there was an increase in the basal metabolic rate in the prepubescent period, reaching its maximum around the time when catamenia was established in girls, and sexual maturity in boys, with a

subsequent decline afterward. There was no uniformity in the height of the increased metabolism or in the duration of the increase. Some of these children had no other symptoms of an enlarged thyroid gland. Others presented such symptoms as enlarged thyroid gland, tremor, nervousness, vasomotor instability, cardiac murmur and tachycardia. All of these symptoms disappeared as the basal metabolic rate returned to the previous normal level, when puberty was well established. The authors feel that an increased basal metabolism is physiologic during pubescence. This increased metabolism coincides with the physiologic age rather than with the chronologic age, and occurs earlier in girls than in boys, coincident with their earlier pubescence. As there seems to be an individual variation in the height and duration of the increased metabolism, it makes the adoption of normal standards difficult for this important age period. The increased basal metabolism may be associated with symptoms simulating organic heart disease or more especially exophthalmic goiter. In evaluating high metabolic figures at this period, the clinical manifestations of pubescence have to be considered. Exophthalmic goiter is rare before puberty and should not be confused with the physiologic overactivity of the thyroid gland in pubescence, which is temporary and the prognosis of which is excellent.

The Seasonal Incidence of Some of the Diseases of Childhood.—HERRMAN (*Arch. Ped.*, 1932, **49**, 73) states that human beings are subject to the same biologic laws as plants and animals. The physical, physiologic and chemical conditions differ at different seasons of the year. The time of greatest susceptibility to many diseases is in the late winter and spring. As several functional neuroses and constitutional conditions, as well as infectious diseases, present this seasonal variation, it seems likely that an increased virulence of infectious material is the primary etiologic factor. The injurious effect seems to depend on a sudden transition or an abrupt change in some meteorologic element. Apparently there are certain persons who are unable to adjust themselves quickly to these changes. Although it is impossible at the present time to be certain what the exciting agent is, it is most likely some form of radiation. Such a hypothesis is supported by the fact that some of the functional neuroses are much more common in some years than in others. Experimental work on laboratory animals would seem to offer the most promising field for a solution of the problem. In such experimentation the various factors involved could be separated, modified and controlled and the effect of different forms of radiation of different wave lengths determined and artificial climates produced. As the vast majority of persons cannot move to a different climate, and as one cannot control to any great extent the air one breathes and the radiation to which one is exposed, efforts must be directed largely to increasing the resistance of the person. This can be done mainly in three ways: The first is by preventing the birth of the defective and the unfit, thus raising the average resistance of the community. The second is by active immunization of infants against the infectious diseases. The third is by providing infants, children and pregnant mothers with a diet containing an adequate amount of vitamins, and by exposing them out-of-doors in the winter and spring so that they may increase their ability to adjust themselves to sudden changes in climate.

DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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Macular Atrophy of the Skin.—CHARGIN and SILVER (*Arch. Derm. and Syph.*, 1931, **24**, 614) review the literature of this rare but interesting dermatologic condition and definitely clarify the issue, proposing the following simple but satisfactory classification:

A. Primary (not preceded by known dermatoses).
   1. Anetodermia Jadassohn.
   2. Anetodermia Schweninger and Buzzi.

B. Secondary (preceded by known dermatoses).
   1. Syphilis (atrophia maculosa syphilitica).
   2. Tuberculosis and lupus erythematoides.
   3. Leprosy.
   4. Other dermatoses.

C. Mixed types of atrophy (macular atrophy and acrodermatitis chronica atrophicans).

The Anetodermia erythematosa of Jadassohn varies greatly in onset and course but for the most part consists of erythematous macular lesions that may pale in the center to form a ring or even become confluent and terminate in atrophic areas with at times a central baglike protrusion which on pressure seems to herniate into the skin. The lesions occur mostly over the trunk and limbs and are found three times more frequently in females than in males. The Schweninger and Buzzi type originally described under the term "multiple benign tumor-like new growths of the skin" differs mostly in the absence of preceding inflammatory changes. Syphilis is by far the commonest cause of secondary macular atrophy. The process may simply be associated with syphilis or, more commonly, replace a previous syphilitic eruption, usually of the papular type. The condition usually appears during the second or third year of a syphilitic infection but much longer time intervals are on record. No entirely satisfactory etiology has been established for the entire group, although the endocrine theory of Singer seems the most plausible. Pathologically the essential changes are fragmentation, contraction and finally disappearance of the elastic tissue.

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF

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Fistula Formation in Cervical Cancer.—In 254 cases of carcinoma of the cervix treated by radium in Cardiff Royal Infirmary, fistulæ have appeared in 22 cases (8.7 per cent) according to STRACHAN (*J. Obst. and Gynec. Brit. Empire*, 1931, **38**, 542). Of the 22 cases, fistula formation occurred only within the last 2 months of life in 8 cases, so that, unless a practically complete follow-up is kept and unless this complication is specifically inquired into, a certain proportion of fistula cases will fail to be included in statistics. In the majority of cases nothing can be done for the fistulæ forming in the course of cervical cancer. Especially is this the case in vesicovaginal fistula and in any fistula when growing carcinomatous tissue occupies its edges. In some few cases in which clinical cure appears to have taken place and when active carcinoma is not present, extreme fibrosis and puckering makes the success of a closure operation problematical at least. Although cure of the fistula is unlikely much may be done in the course of radiation to prevent this complication. Prior to radiation the bowel should be thoroughly emptied and at the completion of irradiation a self-retaining catheter should be inserted and retained during the time that the radium is in position. In this way the bladder and bowel can be kept at a distance from the focus of the gamma rays and out of harm's way. Appropriate packing off of the vaginal walls by gauze soaked in flavine or other antiseptic is also employed. If a flat vaginal applicator is employed, the long diameter of the box should be placed transversely in the pelvis and never anteroposteriorly. In this way not only is excessive anterior or posterior radiation avoided but the lateral fornices and bases of the broad ligaments receive the maximum radiation. Similarly when needles are employed they should not be carried too far toward the anterior or posterior fornices.

Ovarian Neoplasms.—At the Eighth British Congress of Obstetrics and Gynecology which was held at Glasgow in April, 1931, there was presented a very interesting and complete symposium upon the subject of ovarian neoplasms. The contribution which BLAIR BELL (*J. Obst. and Gynec. Brit. Emp.*, 1931, **38**, 249) made to this meeting was concerned with the pathology and clinical features of these tumors. He stated that the relation of age, parity and other points in the histories of the patients and the frequency of unilateral and bilateral neoplasms are worthy of note but they show little difference between innocent and malignant neoplasms. The difficulty in diagnosis arises most commonly in respect to bilateral tumors of a solid or papillary nature,

especially as free fluid is often associated with both the innocent and the malignant. The points to consider are: the presence or absence of a primary malignant growth, masses in the liver, occurrence of adhesions, age and general condition of the patient. Ascites depends on whether the tumor is sufficiently free and out of the pelvis to irritate the peritoneum or whether there are implantations in the general peritoneal cavity. The only treatment considered is surgical. Innocent tumors require removal but an effort should always be made to conserve some normal ovarian tissue. In malignant ovarian disease he is of the opinion that Roentgen rays and radium do more harm than good while chemotherapy with lead may help but it is usually combined with surgery. If the tumor rises above the pelvic brim, laparotomy is advised but attention is drawn to the advantage of the vaginal route for removing cysts in the true pelvis during pregnancy. Long incisions are favored for the larger cystadenomata in people of middle age, owing to the possibility of malignant disease and adhesions, which are more easily separated if the cyst is untapped. He states that it is essential to remove the uterine fundus and both adnexa in all doubtful cases even if localized to one side.

OPHTHALMOLOGY

UNDER THE CHARGE OF

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The Eye Symptoms of Brain Tumors.—According to STÄHLI (*Schweizer. med. Wchnschr.*, 1931, **61**, 702) subjective and objective eye changes are of frequent occurrence and of great diagnostic importance in patients with tumors of the brain. Choked disks are found in about 80 per cent of cerebral tumors and in about 90 per cent of cerebellar and cerebello-pontine angle tumors. Patients with choked disks may complain of transient obscurations of vision, but central vision usually remains good, often for months. It fails earlier in cerebellar than in cerebral tumors. Choked disks are less frequent in metastatic than in primary tumors of the brain. In tumors of the hypophysis, simple descending optic atrophy is more frequent than choked disks. Homonymous hemianopsia occurs in about one-fifth of all cerebral tumors. In almost half the cases it is caused by a lesion involving the occipital lobe. In the rest, some other part of the optic tract is affected. Quadrant hemianopsias are seen less frequently in brain tumors than in softenings following thromboses or hemorrhages. Bitemporal hemianopsia is the result of a lesion involving the optic chiasm and is the classical symptom of tumor of the hypophysis. Binsal hemianopsia is seldom found since a bilateral lesion in the region of the chiasm would be necessary for its production.

Nystagmus is seen much more frequently in tumors of the cerebellum, of the cerebello-pontine angle, and of the fourth ventricle than in those of the cerebrum. Paralysis of the sixth nerve is more frequent in brain tumors than paralysis of the third. Supranuclear lesions of the nerves to the eye muscles are characterized by conjugate paralysis or conjugate deviations. Lateral conjugate paralysis is most common in tumor of the pons. Vertical conjugate paralysis is characteristic of lesions of the corpora quadrigemina and the pineal body. Consideration of the neighborhood signs is often necessary to determine whether the involvement of the third or sixth nerve is at the base of the brain or in the nuclear region. Pupillary changes are not of much value in the diagnosis of brain tumors with the possible exception of lesions in the peduncles or corpora quadrigemina. The fifth nerve is involved most frequently in tumors of the pons and cerebello-pontine angle. Usually the motor portion is not affected. Neuroparalytic keratitis is sometimes associated in tumors of the pons, but rarely in angle tumors. Exophthalmos is seen in about 8 per cent of tumors of the anterior and middle fossa and usually means invasion of the orbit. Occasionally an isolated metastasis in the orbit has been found to be the cause of the exophthalmus. Aphasia and alexia are focal symptoms of a circumscribed lesion of the cerebral cortex, usually on the left side and most often in the occipital lobe.

In tumors of the cerebrum, choked disk occurs in about 80 per cent, simple optic atrophy in about 1 per cent. Vision usually remains good for a long time. Choked disk is most likely to be absent in tumors of the motor region of the cortex, of the convexity of the hemisphere, of the corpus callosum, and of the base, especially metastatic tumors. Tumors arising from the meninges are less apt to cause choked disks than are tumors in the brain substance. Hemianopsia is seen in about one-fifth of the cases and is usually homonymous. In one-half of the cases with homonymous hemianopsia, the tumor is situated in the occipital lobe and in these, visual hallucinations, aphasia or alexia are apt to be associated. Homonymous hemianopsia may also be caused through injury to the optic tract by tumors at the base, in the internal capsule, or in the basal ganglia. Eye muscle disturbances occur in about one-third of the cases, and usually mean a basal lesion. The third nerve is more frequently involved than the sixth. Conjugate paralysis and nystagmus are rare. Isolated fourth nerve paralysis is very rare and usually points to a lesion of the corpora quadrigemina or the pineal region. Involvement of the fifth nerve is rare and is confined essentially to tumors of the base. Exophthalmos is rare.

In cerebellar tumors, choked disks occur in about 90 per cent of the cases and reduction of vision takes place earlier and is of higher degree than in cerebral tumors. Hemianopsia, aphasia and visual hallucinations are not seen except occasionally as secondary pressure effects. Nystagmus and ocular muscle disturbances are much more common than in cerebral tumors. Usually the sixth nerve is involved, more rarely the third; occasionally there is conjugate paralysis or conjugate deviation. The fifth nerve is somewhat more frequently involved than in cerebral tumors. Loss of corneal reflex is frequently an early symptom. Neuroparalytic keratitis is infrequent and exophthalmos is practically never seen.

In tumors of the hypophysis, simple optic atrophy, bitemporal hemianopsia and third nerve paralysis are the characteristic findings. Choked disks occur in about 20 per cent of the cases without acromegaly and less frequently in the cases with acromegaly. Simple optic atrophy is about twice as frequent as choked disk. Bitemporal hemianopsia is found in more than 50 per cent of the cases. Paralysis of the third nerve occurs in about one-fifth of the cases without acromegaly and in one-tenth of the cases with acromegaly. Nystagmus and conjugate paralysis do not occur. Some of the cases with acromegaly show thickening and lengthening of the lids, occasionally with edema, papillomatous formation, or abnormal pigmentation and exophthalmos.

Tumors of the pons are most frequently solitary tubercles, gliomas, or gliosarcomas and are seen often in young people. Choked disks are found in only about one-third of the cases and often not until the late stages. Sixth nerve paralysis occurs in about four-fifths of the cases, is often bilateral, and often accompanied by facial paralysis on the same side. In about one-half the cases, crossed hemiplegia is present. The most characteristic symptom is lateral conjugate paralysis, sometimes bilateral, which occurs in about one-third of the cases, especially when accompanied by crossed hemiparesis, or a complete homolateral facial paralysis. The third nerve is less frequently involved. When present, along with crossed hemiparesis (Weber's syndrome), the tumor has involved the peduncle or the third nerve nucleus. Complete facial paralysis occurs in about one-half the cases—most frequently it is associated with crossed hemiparesis (Millard-Gubler syndrome). Involvement of the fifth nerve is frequent but never isolated. When accompanied by facial paralysis, neuroparalytic keratitis is apt to occur. Nystagmus is not seen.

In tumors of the fourth ventricle, choked disks and nystagmus are more frequent than in tumors of the pons. In acusticus tumors, choked disks are seldom absent. Nystagmus occurs in about one-third of the cases usually with associated cerebellar signs such as ataxia and vertigo. The facial nerve is involved in about one-half the cases. Fifth and sixth nerve paralysis occurs in about one-fourth of the cases. In tumors of the peduncle, often tuberculous, choked disks are rare. Most characteristic is third nerve paralysis with contralateral hemiplegia (Weber's syndrome) or contralateral tremor (Benedikt's syndrome). Tumors in the tegmentum cause oculomotor paralysis with crossed hemianesthesia, and tumors in the fillet, oculomotor paralysis with crossed ataxia.

Tumors of the corpora quadrigemina and pineal region are characterized by paralysis of elevation and depression of the eyes, vertical conjugate paralysis, which is present in about one-fifth of the cases. The third nerve is sometimes involved, sometimes bilaterally; less frequently the fourth or sixth. In about one-fourth of the cases the facial nerve is affected, usually only in its lower branches. Nystagmus is not infrequent. Choked disks occur in about three-fourths of the cases. Involvement of the acoustic nerve is often an important sign.

Christian's Syndrome.—The syndrome characterized by exophthalmos, diabetes insipidus and defects in membranous bones (Christian's syndrome) has been described in about 25 cases under various names,

viz., xanthomatosis, lipemic diabetes, Niemann-Pick's disease and Gaucher's disease. The clinical features of the syndrome are as variable as the histologic picture which has been described under such names as sarcoma, myeloid-sarcoma, myeloid-endothelioma, myxoxanthoma, granuloma, giant cell tumor and giant cell sarcoma. JASON and ABRAHAM (*Am. J. Ophthalmol.*, 1931, **14**, 1146) have observed the course of the disease in a child aged 3 years and 3 months, normal at birth and of healthy stock, who had proptosis of the right eye for at least 19 months; who had lesions of the bones of the skull, shown by Roentgen ray, for at least 14 months, had loose teeth and gingivitis, urine negative, blood cholesterol at the upper limit of normal. The lesion improved under radium treatment.

OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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Regarding Morphological and Functional Changes of the Internal Ear in Arteriosclerosis.—Based on a study of microscopic sections, functional records of hearing, clinical data and autopsy protocols, FABINYI (*Laryngoscope*, 1931, **41**, 663) reported the findings in 26 cases of clinically diagnosed arteriosclerosis—all of which were confirmed at autopsy. Nineteen were males. The ages ranged from 47 to 78 years; 15 were over 60 years of age. In addition to changes in the large vessels elsewhere, the majority showed sclerotic changes in the internal carotid and cerebral arteries. Recognizing arteriosclerosis and "presbyacusia" as normal human involutionary circumstance, the author found that in most instances of marked arteriosclerosis the loss of hearing was greater than in persons with moderate arteriosclerosis; and was usually accompanied by more or less atrophy of the spiral ganglion, the nerve fibers in the osseous spinal lamina and the organ of Corti in the basal coil. In the small bloodvessels of the meatus and modiolus the changes consisted of proliferation of intima and subendothelial tissue, hypertrophy of internal elastic lamina and medial thickening.

Local Lesions in Diphtheria and Their Significance in the Generalized Infection.—Excepting B. tetani, no microörganism pathogenic for man can do so much harm by elaborating a soluble toxin from its local point of attack than B. diphtheriæ. So much so that the Klebs-Loeffler bacillus has come to be regarded virtually as noninvasive or at most only of a feeble local invasiveness; and that the real damage to the human organism results from the systemic dissemination of its powerful exotoxin. Even so, the local pathologico-anatomic features, and to a degree the intensity of the generalized manifestations, of clinical diphtheria can be influenced by several other well-known factors; not the least of which is environment.

For instance, as KIRCH (*Ztschr. f. Laryngol., Rhinol.*, 1931, **20**, 81)

points out that the pseudomembranous lesion caused by B. diphtheriæ is usually less deep and adherent on ciliated columnar epithelium (nasal, laryngotracheal) than on the more commonly involved stratified squamous epithelium of the oropharynx. In other words, less bacillary invasion occurs on ciliated epithelium. From his observations, the author goes on to state that: (1) diphtheria bacilli do not multiply as freely in the blood stream as streptococci or staphylococci; (2) that the disappear from the blood when the local pseudomembrane begins to separate; and (3) Klebs-Loeffler bacilli were found not infrequently in myocardium, kidney, spleen and liver of fatal cases; but not in the nervous tissue. He admits, however, that in many instances no B. diphtheriæ were encountered in degenerated heart muscle.

Abstractor's Comment. Excepting in the overwhelming infections of the agonal period, it is difficult to establish that bacteria actually multiply in the blood stream—even so notoriously invasive forms as anthrax, pneumococci, streptococci, etc. Experimentally, it is well-known that the blood tends to rid itself promptly and thoroughly of enormous doses of pathogenic microbes. All the characteristic cardiac lesions of fatal human diphtheria can be reproduced in the experimental animal by injecting bacteria-free diphtheria toxin.

RADIOLOGY

UNDER THE CHARGE OF
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Chemical Effects of Roentgen Rays.—A large number of dyes were exposed by CLARK and FITCH (*Radiol.*, 1931, **17**, 285) to Roentgen rays under the same conditions of irradiation, to determine, if possible, some of the general types of structures giving good visible color changes. Some of those showing the most promise from the point of view of stability and degree of color change were the triphenyl methane, alizarin, thrazin and indigo types. The magnitude of the field is such that in all probability the color most suitable as an intensity indicator has not yet been found.

Unrecognized Vertebral Fracture versus Kummell's Disease.—The diagnosis of Kummell's disease, or traumatic spondylitis, is being made by roentgenologists with increasing frequency, to the consternation of insurers and industrial accidents boards, often on the unsupported evidence of a solitary wedge-shaped vertebra. The author states that the cause is always trauma, either by direct force against the spine or the impaction of a heavy object on the shoulders and neck. Severe pain in the affected portion of the spine follows but gradually disappears. After a somewhat longer time severe pains recur and motor and sensory

symptoms appear. Still later a definite kyphos and gibbus results. In the opinion of O'BRIEN (*Radiol.*, 1931, **17**, 661) what Kummell has described is unrecognized, hence untreated, fracture of the spine, and presents roentgenograms of illustrative cases.

Traumatic Arthritis.—The most important physiotherapeutic measure for traumatic arthritis is rest, according to KEY (*Arch. Phys. Therap., X-ray, Rad.*, 1931, **17**, 550). Complete rest may be effected by plaster casts, but it must not be continued indefinitely. Partial rest, obtained by supports of elastic, leather or metal, or by protection from strain, such as may be accomplished by altering the shoes or correcting the posture, is often of benefit. Heat, massage and manipulation are popular. Heat and massage relieve pain temporarily and are grateful to the patient, but there is no evidence that they are otherwise beneficial. Manipulation is dangerous, and if used injudiciously may keep a joint sore for many months and result in permanent harm.

The Diagnosis and Treatment of Intestinal Tuberculosis.—For the diagnosis of intestinal tuberculosis, WATSON and CALLANDER (*Arch. Phys. Therap., X-ray, Rad.*, 1931, **17**, 532) consider the roentgenologic examination as most important, and they follow the technique of Brown and Sampson, but often employ the opaque enema in addition to the ingested meal. In the treatment they emphasize the importance of absolute rest in bed. The diet is modified, and the "smooth diet" of Alvarez is often prescribed. Cod-liver oil is given after each meal in a dose of 1 tablespoonful in 3 ounces of tomato juice, served cold, or in orange juice. Solar radiation and the ultraviolet lamp are employed interchangeably. The lamp is used cautiously and a dose of 30 minutes each to back and front at a distance of 30 inches is never exceeded.

Diathermy of the Rectum and Pelvic Colon.—SOPER (*Arch. Phys. Therap., X-ray, Rad.*, 1931, **17**, 545) regards diathermy as the treatment of choice for precancerous polyps, early cancer that projects into the bowel, and simple and tuberculous ulcers of the rectum and pelvic colon. In late inoperable cancer the visible growth can be destroyed and bleeding checked by this means. Adenocarcinoma is by far the most common growth encountered in the rectum and pelvis. The author has destroyed eight such growths in the past 3 years by diathermy without recurrence. Simple ulcers heal quickly. Tuberculous ulcer involving the anal canal responds well to the bipolar method.

Yeast Infection of the Lungs.—Yeast mold infection is rare and usually attacks the skin, according to HEALY and MORRISON (*Am. J. Roentgenol. and Rad. Therap.*, 1931, **26**, 408), but it sometimes gains entrance into the body and produces tubercles, tissue destruction and abscess formation in the lungs, spleen or kidney, and occasionally attacks the meninges and brain. The disease affects all ages, but is found most often after middle life. Blastomycosis is practically confined to Illinois and is found in and about Chicago. Coccidioidal granuloma occurs principally in California and this is also true of torulosis. In mild cases of yeast infection of the lungs the general condition of the patient is good; the sputum is mucopurulent, often scanty, and contains no blood;

physical examination is negative or reveals only a few râles; the condition may last for weeks or months and go on to spontaneous cure or turn into the severe type. The severe type closely resembles phthisis. The patient becomes emaciated, has a hectic fever, and the expectoration is often hemorrhagic. At times the sputum has a yeasty odor. The roentgenologic picture is similar to that of tuberculosis. The diagnosis is based on the absence of tubercle bacilli and the presence of yeast cells in the sputum. It is essential that the sputum be collected in sterile receptacles after the patient has gargled with warm sterile water, and the specimen must be examined immediately. The authors have observed 5 cases. In the first case, their attention was attracted by the disparity between the appearance of the patient and the extent of the lesion shown by the roentgenograms. From the roentgenogram he should have been very ill, but he was only a little below par. Saccharomyces busse was found in the sputum. The 4 other cases clinically followed a course similar to tuberculosis, and this was the tentative roentgenologic opinion in several. The yeast fungi found in all cases were of the Blastomycetes imperfecti class, of the genus Oïdium.

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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Inheritance of Mental Characteristics.—East (*Mental Hygiene*, 1931, **15**, 45) states that normal mentality and feeblemindedness are a pair of contrasting unit characters inherited as if the difference between them were due to a single unit of heredity, a single gene. Thus the basis upon which the geneticist constructs his concept of the inheritance of mental attributes is obvious. Inheritance in man has been found to be the same as in any other sexually reproducing organism. And there is plenty of evidence to show that mental traits are transmitted in precisely the same manner as other traits. The normal variability in general intelligence and in special aptitudes, which is shown in every population group, is intelligible only on the assumption that a limited number of genes have varied into what one may call the plus and minus types. It is impossible to determine the number of such mutations because genes are not unite in their action; one particular gene may have 100 times as much influence in altering intelligence as some other particular gene. Yet it is unnecessary to postulate mutations in any great number of genes to account for the variability in human mentality that is actually observed. From 20 to 40 mutations would be ample. Twenty plus and 20 minus genes affecting mentality would give the opportunity for over 1 million gene patterns in the germ cells. Theoretically, it would be possible for any one of these genes to mutate to a

type that would produce a breakdown in the mental machinery. Under such conditions normal mentality and defective mentality would behave as so-called unit characters in crosses; that is to say, they would behave as if the difference followed the distribution of a single gene. And the defective mentality could exist in numerous grades, due to action of the other genes that go to make the physical basis of the mind; just as normal mentality can exist in numerous grades for similar reasons.

Contribution to the Differential Diagnosis of Epileptic Disorders.—Baum (*München. med. Wchnschr.*, 1931, **78**, 25) presents a patient in whom the symptoms had been regarded for years as due to an idiopathic epilepsy, despite the late age of onset of attacks. The mildness of the original head injury and the symptomless interval of 2 years allowed the traumatic basis to be overlooked. The patient was a man, aged 38 years, who, while serving during the World War in the Landwehr, was admitted to a hospital in November, 1914, on account of head wounds from a hand grenade. Minor injuries of the right cheek and lower jaw were present and the patient was discharged by Christmas. He returned to the line where he remained perfectly well until July, 1917, when he suffered from an epileptic fit. He remained under medical observation at various hospitals during the next 8 months and was finally discharged from the army in March, 1918, with a pension of 33⅓ per cent. Epileptic attacks of a mild character continued, at intervals varying from 1½ to 4 weeks, being more frequent when he worked hard. As he had injured himself on many occasions, he found difficulty in obtaining employment and in August, 1930, he sought an increase in the amount of his pension. He was accordingly admitted to a hospital, where no neurologic abnormality was detected. His mentality was characterized by dullness, slowness of cerebration, inattention and irritability. One or two insignificant scars were apparent over the cheek and right side of the head. A Roentgen ray revealed a large number of small, irregular metallic splinters embedded in the soft tissues of the right side of the face and in the right hemisphere. A number lay in the region of the scalp wound, and two larger fragments were visible in the depths of the right parietoöccipital lobes.

A Pathologic Contribution to the Concept of Neurosomatic Deterioration in Epilepsy, With Record of Two Cases.—Hodskins and Yakovlev (*Am. J. of Psychiat.*, 1931, **10**, 663) present 2 cases which clinically, seem quite different; however, both show the same essential features: epilepsy and the symptomatologic pattern of neurosomatic deterioration. In the first case, that of a child, deterioration developed more rapidly and was more destructive, in 9 years leading to the ultimate stage of neurosomatic deterioration, viz., profound dementia and cerebral flexion paraplegia. In the second case, that of a man aged 66 years, with late epilepsy, the neurologic picture characteristic of neurosomatic deterioration developed more slowly, was not so dramatic, and the symptomatologic pattern was one that could be identified with arteriosclerotic Parkinsonism. Pathologically, in both cases was found evidence of a primary vascular cerebral lesion, which was, in the first case, an acute lesion, viz., meningioencephalitis; in the second case, a chronic lesion, viz., cerebral arteriosclerosis. In both the primary pathologic

lesion was the starting point of the same chronic degenerative process affecting principally the frontal cortex (third layer and basal ganglic pallidum and peduncular hypothalmic formation). This last chronic degenerative and atrophic secondary process seems to be the most plausible cause of the clinical symptoms of neurosomatic deterioration. The predominant localization of this process in the third layer of the cortex and the globus pallidus appears to agree with the fundamental features of the clinical syndrome which was manifested by disturbances in the psychomotor sphere, viz., dementia and progressive rigidity.

Epilepsy as an Exaggerated Form of Normal Cerebral Inhibition.—ROSETT (*Am. J. of Psychiat.*, 1931, **10**, 673) states that the phenomena of the seizure, whatever the indirect underlying cause may be, are directly caused by that process of interference of nerve impulses, with the result of their mutual extinction, which is known as inhibition. Such inhibition is in itself a normal process, to which the phenomena of thought, imagery and dreams owe their existence. Even under normal conditions there is a wide range in the degree of facility with which cerebral inhibition takes place, thus making for the fact that some persons can exert their powers of attention with greater intensity than can other persons. Any condition that will disturb the chemical, physical or mechanical balance of the nervous system, may result in a aci litation of the normal process of cerebral inhibition, with the appearance of epileptic seizures as a result.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF
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Tumors of the Suprarenal Gland With Special Reference to Carcinoma of the Cortex: Report of a Case.—MEYER and FRUMMES (*Arch. Int. Med.*, 1931, **48**, 611) have presented a case of a girl, aged 13 years, who suffered from a malignant tumor of the suprarenal cortex, and who exhibited some of the characteristic symptoms of the genito-suprarenal syndrome seen with tumors of the suprarenal cortex with neoplastic tendencies. The case report is followed by a review and discussion of the subject with special reference to the diagnostic symptoms composing this syndrome, and the prognosis and the treatment of such cases. Another section of the paper deals with the pathology of tumors of the suprarenal gland.

Tumors of the Heart and Pericardium: Pathology, Symptomatology and Report of 9 Cases.—YATER (*Arch. Int. Med.*, 1931, **48**, 627) presents a comprehensive review of the subject of primary and secondary tumors of the heart and pericardium; and points out that these tumors

are rare and the majority are without symptoms and are therefore of interest only to the pathologist. He discusses the symptomatology under these two headings: clinical types not suggestive of tumor of the heart; and clinical types suggestive of tumor of heart. Over 150 cases of primary tumors of the heart have been reported in the literature and about 20 per cent of these were malignant. "Primary tumors of the heart are myxoma, fibroma, sarcoma, rhabdomyoma and less commonly lipoma, endothelioma and a few rare forms. Varices occur in the heart, and nodular leukemic infiltrations are occasionally seen." Primary tumors of the pericardium are usually sarcoma or lipoma. Secondary tumors of the heart show a great variation in type, size and distribution; the lesions are usually carcinomatous or sarcomatous. The primary growth may occur in any organ. The author gives a detailed report of 9 cases of tumor of the heart and mentions 2 additional cases of later observation.

On the Susceptibility of the Gopher (Citellus Tridecemlineatus) to Mycobacterium Tuberculosis.—Feldman (*Am. J. Path.*, 1931, **7**, 139) reports that with the use of original strains of the Mycobacterium tuberculosis derived from human bovine and avian sources, using either the subcutaneous, intraperitoneal or intravenous routes of injection, he succeeded in infecting the striped gopher with each of the three bacillary forms. The animals died at intervals of from 36 to 78 days; or were sacrificed from 40 to 91 days after inoculation. Definite lesions of tuberculosis were observed as a consequence of each of the three forms of the tubercle bacillus. The animal appears to be more susceptible to the human and bovine types of the tubercle bacillus than to those derived from avian sources. The degree and extent of infection varied with the route of inoculation, being most pronounced in the animals inoculated intravenously. The histopathology of the lesions produced by the three types of tubercle bacillus in this animal is essentially of the same character. It is interesting that this animal is, to some degree at least, susceptible by the ordinary routes of injection to the avian strain.

Silicosis and the Effect of Silica on the Growth of the Tubercle Bacillus.—The well-known fact that patients with silicosis practically always succumb to pulmonary tuberculosis makes particularly interesting the cultural results of Price (*Proc. Exper. Biol. and Med.*, 1931, **28**, 819) who reports that the addition of 1 cc. of sodium silicate or silicic acid, standardized to contain 1 mg. silica, to every 100 cc. of modified Dorset's egg medium enhances the growth and development of the tubercle bacillus in the test tube. This is apparent by a lessening of the latent period and a greater luxuriance of growth. The stimulating effect of these silicon compounds is continuous throughout the whole period of growth. These observations cover 20 initial cultures of the tubercle bacillus, isolated indirectly through guinea-pig inoculation or directly from human sources as urine, sputum, pus, cerebrospinal fluid, and in one instance ascitic fluid. Colonies have been observed in 6 to 9 days; growth continues rapidly, and in some instances can be considered luxuriant in 3 weeks, or even less.

Idiopathic Fevers and Agglutination Tests With Brucella Abortus Antigen.—From a study of a large number (3716) of blood serums made in the various Public Health Laboratories of the State of New York. BAYNE-JONES (*Am. J. Pub. Health*, 1930, **20**, 1313) in a search for unsuspected cases of undulant fever found that 64 (1.72 per cent) gave agglutination with Brucella abortus antigen in a dilution of 1 in 100 which was considered diagnostic. In 10 cases of typhoid fever the serum gave agglutination reactions using this same antigen in dilutions of 1 in 10 to 1 in 40—not diagnostic. On the other hand 180 specimens from patients suspected of having typhoid fever were entirely negative. The result of this study seemed to indicate a fairly high degree of specificity for the reaction. Farming and occupations associated with farming and cattle raising were those most frequently correlated with positive reactions for undulant fever in this series. It is suggested that valuable information will be obtained if this test is done routinely on the serum of patients suffering from obscure and periodical fevers, arthritis, abdominal and intestinal disorders as well as of cases suspected of having typhoid fever or tuberculosis. The widespread occurrence of the disease in New York State would suggest that this disease should be thought of in all febrile conditions.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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A Bacteriologic Study of "Colds" on an Isolated Tropical-Island (St. John, United States Virgin Islands, West Indies).—MILAM and SMILLIE (*J. Exper. Med.*, 1931, **53**, 733) report investigations which form a part of a study of colds in isolated communities under different environmental conditions. Previous studies have been made in Alabama and Labrador, and this third group was conducted in St. John, one of the Virgin Islands. Two arresting facts were noted in the last studies: (1) The mild type of colds that were encountered; (2) the constancy and uniformity of the bacteriologic flora of the nasopharynx. If the previous studies in Labrador and Alabama are considered in conjunction with the St. John studies, it is noted that certain flora of the nasopharynx are found consistently in uniform numbers in all areas. The results suggest that colds are incited by some specific agent with which we are not as yet familiar. They suggest also that the secondary and more severe symptoms associated with colds may be due to certain aërobic flora commonly found in the nasopharynx. Types of pneumococci which are virulent (to white mice) and true Pfeiffer's bacilli requiring both V and X substance (and forming indol?)

seem to be of particular importance in these secondary infections. The studies indicate that the specific agent which initiates colds is infectious in nature, and spread by direct contact, with an incubation period of 1 to 3 days. There is strong evidence that environmental factors, particularly reduction in atmospheric temperature, have some influence upon the incidence of colds. The investigations indicate that colds are less common and much less severe in the tropics than in the temperate zone. The basic nasopharyngeal flora in normal persons in St. John is similar to that of normal persons in Labrador and Alabama. Pfeiffer's bacilli are much less common in St. John than in the temperate zone. Hemolytic staphylococci are prevalent in the tropics, hemolytic streptococci are rare. Pneumococci are prevalent in St. John but are avirulent. Fixed Types I, II and III are rare. The basic nasopharyngeal flora in St. John was quite constant throughout all seasons and in all groups of people. No change occurred in the nasopharyngeal flora in a group of persons who developed colds. The seasonal incidence curve of acute colds in St. John was a replica in miniature of the same curve for the United States. No colds occurred during the very warm period from June to October. An epidemic of colds in December was coincident with a slight but abrupt drop in atmospheric temperature.

Points to be Considered in Case of a Poliomyelitis Epidemic.—LEAKE (*U. S. Pub. Health Rep.*, 1929, **44**, 1819) considers 3 weeks a suitable period of quarantine, especially since the patient needs rest for that period. He regards healthy, acute, rather than chronic carriers as the most usual means of spread. Diminishing human contacts in general is advocated, but the closing of places of assembly is not advocated under ordinary conditions. Organization for treatment of preparalytic cases by convalescent serum is important, but it is pointed out that the method is still on trial. With respect to after treatment the following is said: Probably the greatest good that the State Department of Health can do is in the prevention of deformities and crippling as an aftermath of recognized paralytic cases. The early treatment should certain be under the control of the local physician. In connection with the circularization and publicity, to aid in the early diagnosis, emphasis should be placed on the necessity of absolute and prolonged rest in bed, in a position to forestall and prevent any tendency to deformity, by fixation if necessary. There comes a time in practically every case, however, and it may come very soon, when the proper care becomes too irksome for the family to carry on without the moral support and stimulus of some such agency as a consultant orthopedist with nurses or physiotherapists particularly skilled and trained in this disease; and it is a rare family which can afford the expense of such prolonged, continuous and special skill unless the treatment is supervised under some such auspices as those of the state or municipal department of health. Adequate hospitalization of these cases is out of the question.

The Pyrogenic Reaction to Concentrated Antipneumococcus Serums, with Respect to Certain Serum Constituents.—FELTON and KAUFFMANN (*J. Exp. Med.*, 1931, **49**, 337) studied the nature of the protein with which antibody of the pneumococcus obtained from immune horse serum is associated to find, if possible, any differences that may exist

between preparations that are satisfactory on intravenous injection and those that produce chills or other untoward reactions. From the results of the investigations with preparations made by three different methods, the authors draw the following conclusions: (1) Chill-producing lots still contain some material precipitable at a pH value of from 4.8 to 5.2 in a neutral salt concentration which is about one-twentieth normal, whereas under these conditions good preparations contain but little. (2) Chill-producing lots have a slightly higher phosphorus and perhaps a higher lipoid content than good ones; the differences are so slight, however, as to indicate that the residuum of these agents in the final preparations may not be responsible for pyrogenic action. Unsatisfactory preparations contain more ammonia and nonprotein nitrogen than do those that are suitable for intravenous injection.

The Movements of Epidemic Meningitis,—1915-1930. — HEDRICH (*U. S. Pub. Health Rep.*, 1931, **46**, 2709) reviews some of the general epidemiologic characteristics of epidemic meningitis, and the recent movements of the disease as to time and place. The available evidence indicates that during epidemics surprisingly large proportions of the population may at one time or another become infected with the meningococcus. Under highly congested conditions, as in army camps, it appears that practically the entire population may become infected once or oftener during epidemics. Probably far less than 1 per cent of such infections result in clinical attack, as annual attack rates in excess of 1 per 1000 population are rare. The case fatality, however, is heavy; approximately one-half of the reported cases died during the recent epidemic, in spite of fairly widespread use of serum. Meningitis became increasingly prevalent in Europe shortly after the opening of the World War, and in the United States shortly after her entry, when mobilization began. The highest attack rates in England came in 1915 and in the United States in 1918. In 1928–1930 the disease was again epidemic in most parts of the world. The interval between the last two epidemic maxima was 11 years in the United States and a few years longer in most European countries. The interepidemic interval is highly variable. It has oftenest been 6 to 12 years, but some areas have run as long as 25 years without epidemics. Massachusetts, for example, has had no appreciable epidemic since about 1905, and New York City only a minor one, namely, in 1928–1930. Over broad areas, such as large groups of states, epidemics have appeared, not as sporadic explosions but as crests of rather smooth and systematic waves, the rising and declining phases of which have covered a period of 3 to 6 years or longer. Within smaller areas, such as individual cities, the movements of the disease have been less systematic. Neither of the last two epidemics was synchronous in different parts of the United States, some regions having lagged 2 years behind others. The time rate of epidemic development within specific areas and the rate of geographic movement are very much slower for meningitis than for influenza. In the 1918 epidemic the reported attack rates were highest in the southern sections, probably due to the large number of military concentration camps; the Rocky Mountain States had the lowest rates. In the 1928 outbreak the Southern States had the lowest and the Mountain States the highest rates.

Typhus Fever: The Rat Flea, Xenopsylla Cheopis, in Experimental Transmission.—DYER and his associates (*U. S. Pub. Health Rep.*, 1931, **46**, 1869) claims that on epidemiologic grounds there is an association between typhus fever and the handling of foodstuffs and rats. In the present experimental work the tropical rat flea was shown to be able to convey typhus infection from one white rat to another.

Three Outbreaks of Food Poisoning Apparently Due to Bacillus Enteritidis, Bacillus Paratyphosus B (Aertrycke Type) and Bacillus Paratyphosus A, Respectively.—GEIGER and his associates (*U. S. Pub. Health Rep.*, 1931, **46**, 1565) found the incubation period in each of the outbreaks to be 2 to 4 hours, which, together with the relatively short duration of symptoms, indicate preformed toxins rather than infections. In the outbreak due to B. enteritidis the source was considered as most likely to be incompletely cooked veal. In the case of B. paratyphosus B infections the source was considered to be rice pudding and this was probably infected by a commercial rat virus. In the outbreak due to B. paratyphosus A a human carrier was the most probable source and an egg-shouffle-shrimp mixture was the means of transmission from the carrier to the victims.

PHYSIOLOGY

PROCEEDINGS OF
THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA
SESSION OF MARCH 14, 1932

Heterochronism in the Single Fiber Nerve Muscle Complex.—H. GRUNDFEST (from the Eldridge Johnson Foundation for Medical Physics, University of Pennsylvania). The question of isochronism between muscle and nerve has been studied in the single fiber nerve muscle complex of the retrolingual membrane. The single fiber preparation has several advantages over the gross preparation. The measurements obtained are, first of all, free from the statistical averaging which occurs when a large number of fibers are used. Also, on direct stimulation only the muscle fiber stimulated responds while the entire motor unit responds to indirect stimulation through the nerve. It is, therefore, possible to distinguish very clearly between the two types of stimulation.

The results obtained indicate that the law of isochronism is not valid for the retrolingual preparation. Furthermore, Lapicque's theory regarding curarization does not apply to this preparation, since curari does not affect the chronaxie of muscle fibers. These results are in accordance with the work of Lucas and of Rushton. This agreement is strengthened by the fact that compound curves of the type described by these observers can be obtained from the retrolingual preparation. In this case, as already pointed out, it can be demonstrated directly that a break in the strength duration curve is accompanied by a change to a new excitable element. The suppressed portions of the two components of the compound curve are also obtainable.

Data have also been obtained which cast doubt upon the value of chronaxie as a concept. The chronaxie is found to vary with size of electrode and with structural modification of the excitable tissue. It is, therefore, impossible to speak of a definite experimentally measurable chronaxie and unwise to apply the chronaxie concept to theoretical speculation.

The Effect of Different Salts on the Swelling of Lipoids.—M. SPIEGEL-ADOLF (from the D. J. McCarthy Foundation for Neurological Research, Temple University). With reference to the important rôle that the abnormal swelling of the brain plays in nervous diseases, the following experiments were made with the purpose of enabling *in vitro* studies of the effects of therapeutics on lipoids. According to the method of Keeser, the lecithin sols were made out of egg lecithin of Merck. The viscosity of such solutions was studied by the method of Ostwald. In conformity with the results of Handovsky and Wagner, the depressing effect of neutral salts on lecithin sols could be demonstrated. But, while those authors missed any influence of hypnotics on the viscosity, it could be shown that the latter was much more lowered by the addition of bromid than by any other neutral salt, including thiocyanate and the salt mixtures used by Pierre Marie in the treatment of epilepsy. The results became only more distinct when protein was added to the mixture of lecithin sol and salt. Different proteins seemed to behave in a different way. The greatest effect could be observed in pseudoglobulin. The marked effect of bromid on the viscosity of lecithin sols could not be explained by the law of Hofmeister, according to which iodin and thycocyanate ions should be more efficient. But it could be observed that KI containing some free iodin had a greater influence on the viscosity than the pure salt. So it was suggested that the effect of the bromid salt was due to the action of the oxydized bromin, perhaps on the group of unsaturated fatty acid in the lecithin molecule. In fact, measurements of the refraction of lecithin and lecithin salt mixtures by the interferometer of Zeiss seem to agree fairly well with this hypothesis. It could be demonstrated that, while the refraction of a lecithin KCl mixture was almost exactly equal to the sum of the interferometric values of the single components, addition of KBr and of KI, especially when the latter contained free iodin, seemed to increase the interferometric value of lecithin. These results, which are in conformity with those obtained by the viscosity measurements, point to the close relations between chemical and colloid chemical properties in colloids. Preliminary investigations have further shown that a reaction of drugs used as hypnotics with lecithin could be detected by changes of the refraction, while they were missed in a case in which a poison inducing convulsions was added to the lecithin sol.

The Central Mechanism of Tonic Spasms, Rigor and Catalepsy, Produced by Toxins.—E. SPIEGEL (from the D. J. McCarthy Foundation for Neurological Research, Temple University). The tonic spasms following extirpation of the parathyroids are observed even after a transverse section of the brain stem behind the nucleus ruber and

after extirpation of the cerebellum (Spiegel and Nishikawa). The spinal cord, medulla oblongata and pons are sufficient for the genesis of such spasms.

The rigor observed in narcosis is only partly due to paralysis of the cortex. After one-sided injuries of the motor area, the frontal, or the temporal lobe, this rigor is more marked in the extensor muscles of the opposite side (Spiegel and Bernis, Spiegel and Hotta). A bilateral action of the toxin upon subcortical apparatus is here combined with the one-sided increase of the excitability of such mechanisms, due to the one-sided cortical injuries. The development of the local rigor in tetanus poisoning depends upon impulses from higher centers to the spinal cord. This rigor is less marked on the side of a hemisection of the spinal cord; in animals (rats and cats) whose corpus striatum had been extirpated a form of flexor rigidity develops instead of the extensor rigidity, whereas the destruction of the cortex has no such influence. (Spiegel and Bruwer.)

On the other hand, the increase of tonicity produced by bulbocapnin is influenced by cortical impulses. The injection of this poison in cats whose motor area had been destroyed on one side produces asymmetries of the posture of the limbs and a torticollis-like posture of the head, which are missed after the operation on the cortex alone. (Spiegel and Krisch.)

The diminution of voluntary movements in the so-called bulbocapnin catalepsy is not due to paralysis of the cortex, as the excitability of the motor area is not lowered by such doses of bulbocapnin as are sufficient to produce the catalepsy. This fact, and the observation that larger doses of bulbocapnin produce symptoms of central, especially cortical stimulation (Schaltenbrand, De Jong), lead to the assumption that the bulbocapnin catalepsy is due to a central inhibition, as a consequence of weak stimulation of the forebrain. As small doses of poisons acting mainly upon the cortex (like small doses of cocain) produce, at the most, only very slight cataleptiform reactions, one might assume that the catalepsy in bulbocapnin poisoning is due to the action of this poison, not only upon the cortex, but also upon subcortical ganglia of the forebrain. One can break through the central inhibition in bulbocapnin catalepsy by the inhalation of CO_2–O_2 mixtures (Spiegel and Kaufman), or by the injection of larger doses of cocain (Spiegel and Evrard), thus producing an effect of these poisons similar to that observed in stuporous patients.

The Study of the Heart Action With the Roentgen Cinematograph.—W. Edward Chamberlain (from the Laboratory of Radiology, Temple University). The Roentgen cinematograph, as designed and built by by Dr. H. E. Ruggles, of the University of California, is a device which enables us to obtain serial instantaneous teleroentgenograms of the beating human heart at the rate of exactly 15 per second. Such serial teleroentgenograms have been photographed onto motion picture film, and the resulting cinematographic demonstration is of great interest to the cardiac physiologist.

Using Dr. Ruggles' device, we obtained serial roentgenograms of normal cases and cases with mitral stenosis and mitral regurgitation.

By means of careful measurements upon such serial films we have plotted the movements of various parts of the cardiac silhouette upon a time scale. The resulting curves, which have become known as skiacardiograms, are of great interest from the standpoint of the physiology and pathology of valvular disease, and a comparison of our findings with postmortem studies has suggested that the method is capable of being put to clinical use.

This presentation consists of a demonstration of the motion picture of the normal beating heart, followed by a lantern slide demonstration of the method of exposing and measuring the films, and a series of typical skiacardiograms of normal and diseased hearts. Skiacardiographic curves bear a closer resemblance to myographic tracings of heart muscle than to volume curves obtained with the plethysmograph.

The simplicity and economy of the "slit method" of "Roentgen kymography" recommend that procedure for the study of movements of the borders of the heart shadow, but there are technical difficulties in the way of accurately locating the observed points upon the cardiac silhouette. The chief advantages of our method lie in our ability to definitely identify the part of the cardiac silhouette whose motion we are studying and to obtain simultaneous graphs of the movements of all parts of the silhouette for the same heart cycle.

REFERENCES.

Chamberlain, W. E., and Dock, W.: The Study of the Heart Action with the Roentgen Cinematograph, Radiology, 1925, **7**, 185.

Chamberlain, W. E., and Dock, W.: Motion of the Heart in Disease of the Mitral Valve, Arch. Int. Med., 1927, **40**, 521.

Correction

In the paper entitled "Iodin in Exophthalmic Goiter," by Jacob Lerman, M.D., and James H. Means, M.D. (this Journal, 1931, **181**, 750), the second paragraph should read as follows: "The average basal metabolism just after admission to the hospital was +57. After a resting period varying from 2 to 9 days the average basal metabolism was +53. After treatment with ethyl iodid it was +24. The average daily fall in metabolism was 3.7 points, varying from 1.8 to 7.4."

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